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L3	condition$ medi$	9022	L3
L2	endothelial mitogen or VEGF$	4927	L2
L1	endothelial cell line or HUVEC	3529	L1

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NEWS 21 Jun 06 Simultaneous left and right truncation added to CBNB
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=> s VEGF A or VEGF C
L1 1907 VEGF A OR VEGF C

=> d bib abs

L1 ANSWER 1 OF 1907 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:325713 BIOSIS
DN PREV200300325713

TI UTILIZATION OF DIFFERENT CELLULAR MECHANISMS TO SCREEN FOR NEUROPROTECTIVE
COMPOUNDS FOR STROKE.
AU Pong, K. (1); Bramlett, D. R. (1); Zaleska, M. M. (1)
CS (1) Neuroscience, Wyeth Research, Princeton, NJ, USA USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 694.16. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002 Society for Neuroscience

DT Conference
LA English
AB The neuropathology following ischemic stroke results from multiple cellular and molecular mechanisms. Development of efficacious therapeutic compounds for stroke must address some, if not all, of these mechanisms. Therefore, we utilized different assays, which address different mechanistic pathways, to screen for neuroprotective compounds for stroke. To examine excitotoxicity, cerebellar granule neurons (CGNs) were cultured from post-natal day 7 rat pups and maintained for 14 days in vitro prior to experimentation. Mature CGNs were subjected to 4-hr of oxygen glucose deprivation (OGD), resulting in 50-60% cell death, as determined by lactate dehydrogenase release. Treatment with MK-801 provided significant protection against OGD-induced cell death. As a model of apoptosis, CGNs were deprived of potassium. Decreasing potassium levels from 25 mM to 5 mM, resulted in 50% apoptosis over a 24-hr period. Treatment with cycloheximide or DEVD-CHO afforded significant protection. Brain edema develops as a result of increased vascular permeability (VP). Vascular endothelial growth factor (***VEGF***), ***a*** potent mediator of VP, may contribute to brain edema, via Src kinase activation. By blocking Src activity, VP and brain edema are prevented. To mimic this signaling cascade, we utilized human umbilical vein endothelial cells (HUVECs). HUVECs grown under serum free conditions undergo apoptosis, while cells treated with VEGF do not. The co-administration of the Src kinase inhibitor PP2 blocks VEGF activity, suggesting the involvement of Src. Taken together, these assays provide the foundation for a feasible screening methodology for neuroprotective compounds for stroke.

=> s VEGF A and VEGF C
L2 163 VEGF A AND VEGF C

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 81 DUP REM L2 (82 DUPLICATES REMOVED)

=> d bib abs

L3 ANSWER 1 OF 81 CAPLUS COPYRIGHT 2003 ACS
AN 2003:282828 CAPLUS
DN 138:298132
TI Modulators of VEGF or VEGFR binding to neuropilin-2, materials and methods for detecting said modulators, and therapeutic uses of the modulators.
IN Alitalo, Kari; Karkkainen, Marika; Karila, Kaisa
PA Ludwig Institute for Cancer Research, USA; Licentia Ltd
SO PCT Int. Appl., 181 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003029814	A2	20030410	WO 2002-EP11069	20021001

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003113324	A1	20030619	US 2002-262538	20020930
PRAI US 2001-326326P	P	20011001		

AB The present invention relates to identifying modulators of ***VEGF*** - ***C*** binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators. A method of screening for modulators of binding between a neuropilin growth factor receptor and a ***VEGF*** - ***C*** polypeptide is claimed comprising steps of: (a) contacting a neuropilin compn. with a ***VEGF*** - ***C*** compn., in the presence and in the absence of a putative modulator compd.; (b) detecting binding between the neuropilin polypeptide and the ***VEGF*** - ***C*** polypeptide in the presence and absence of the putative modulator compd.; and (c) identifying a modulator compd. based on a decrease or increase in binding in the presence of the putative modulator compd. as compared to binding in the absence of the putative modulator compd. The neuropilin receptor compn. comprises a neuropilin receptor extracellular domain fragment bound to a solid support or a neuropilin receptor extracellular domain fragment fused to an Ig Fc fragment. The ***VEGF*** - ***C*** compn. comprises a purified mammalian prepro- ***VEGF*** - ***C*** polypeptide or a fragment. A method of screening for modulators of binding between a

neuropilin growth factor receptor and a VEGFR-3 polypeptide is also claimed. The VEGFR-3 compn. used in the method comprises a receptor extracellular domain fragment bound to a solid support or a receptor extracellular domain fragment fused to an Ig Fc fragment. Addnl. claimed is a method for screening for selectivity of a modulator of ***VEGF*** - ***C*** , VEGFR, or neuropilin biol. activity. A method of modulating growth, migration, or proliferation of cells, specifically neurons, in a mammalian organism by administering a compn. comprising a neuropilin polypeptide or fragment, and a ***VEGF*** , ***a*** PIGF, a semaphorin, or a bispecific antibody specific for the neuropilin receptor and for a ***VEGF*** - ***C*** polypeptide or for a neuropilin receptor and a VEGFR is also claimed.

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FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 18:36:48 ON 16 JUL 2003
L1 1907 S VEGF A OR VEGF C
L2 163 S VEGF A AND VEGF C
L3 81 DUP REM L2 (82 DUPLICATES REMOVED)

=> s l3 and MTS
L4 1 L3 AND MTS

=> d bib abs

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN 2002:276183 CAPLUS
DN 136:289910
TI Plasmid vector carrying endothelial cell mitogen for gene therapy and assay for cell survival of transiently transfected cells
IN Kearney, Marianne; Isner, Jeffrey M.
PA St. Elizabeth's Medical Center, USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002029082	A1	20020411	WO 2001-US29638	20010921
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001094633	A5	20020415	AU 2001-94633	20010921
US 2002155421	A1	20021024	US 2001-961128	20010921
PRAI US 2000-236767P	P	20000929		
WO 2001-US29638	W	20010921		

AB The present invention provides novel methods for detg. the bioactivity of a plasmid encoding for an endothelial cell mitogen. The invention also provides a method to optimize a plasmid construct for use in a gene therapy procedure. Further, the invention provides a quant. quality control assay for evaluating a batch of plasmid DNA prior to use in a gene therapy treatment. The said endothelial cell mitogens include acidic and basic fibroblast growth factor, VEGF, EGF, transforming growth factor .alpha. and .beta., platelet-derived growth factor, platelet-derived endothelial growth factor, tumor necrosis factor, hepatocyte growth factor and insulin-like growth factor.
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FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 18:36:48 ON 16 JUL 2003
L1 1907 S VEGF A OR VEGF C
L2 163 S VEGF A AND VEGF C
L3 81 DUP REM L2 (82 DUPLICATES REMOVED)
L4 1 S L3 AND MTS

=> s l3 and (HUVAC and Cos)
L5 0 L3 AND (HUVAC AND COS)

=> s l3 and HUVAC
L6 0 L3 AND HUVAC

=> s l1 and biological activ?
L7 16 L1 AND BIOLOGICAL.ACTIV?

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 10 DUP REM L7 (6 DUPLICATES REMOVED)

=> d bib abs 1-
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L8 ANSWER 1 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:254065 BIOSIS
DN PREV200300254065
TI A set of loop-1 and -3 structures in the novel vascular endothelial growth factor (VEGF) family member, VEGF-ENZ-7, is essential for the activation of VEGFR-2 signaling.
AU Kiba, Atsushi; Yabana, Naoyuki; Shibuya, Masabumi (1)
CS (1) Division of Genetics, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokane-dai, Minato-ku, Tokyo, 108-8639, Japan: shibuya@ims.u-tokyo.ac.jp Japan
SO Journal of Biological Chemistry, (April 11 2003) Vol. 278, No. 15, pp. 13453-13461. print.
ISSN: 0021-9258.
DT Article
LA English
AB The vascular endothelial growth factor (VEGF) family plays important roles in angiogenesis and vascular permeability. Novel members of the VEGF family encoded in the Orf virus genome, VEGF-E, function as potent angiogenic factors by specifically binding and activating VEGFR-2 (KDR). VEGF-E is about 45% homologous to ***VEGF*** - ***A*** at amino acid levels, however, the amino acid residues in ***VEGF*** - ***A*** crucial for the VEGFR-2-binding are not conserved in VEGF-E. To understand the molecular basis of the ***biological*** ***activity*** of VEGF-E, we have functionally mapped residues important for interaction of VEGF-E with VEGFR-2 by exchanging the domains between VEGF-ENZ-7 and PIGF, which binds only to VEGFR-1 (Flt-1). Exchange on the amino- and carboxyl-terminal regions had no suppressive effect on ***biological*** ***activity*** . However, exchange on either the loop-1 or -3 region of VEGF-ENZ-7 significantly reduced activities. On the other hand, introduction of the loop-1 and -3 of VEGF-ENZ-7 to placenta growth factor rescued the ***biological*** ***activities*** . The chimera between ***VEGF*** - ***A*** and VEGF-ENZ-7 gave essentially the same results. These findings strongly suggest that a common rule exists for VEGFR-2 ligands (VEGF-ENZ-7 and ***VEGF*** - ***A***) that they build up the binding structure for VEGFR-2 through the appropriate interaction between loop-1 and -3 regions.

L8 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2003:106870 BIOSIS
DN PREV200300106870
TI Pseudocowpox virus encodes a homolog of vascular endothelial growth factor.
AU Ueda, Norihito (1); Wise, Lyn M.; Stacker, Steven A.; Fleming, Stephen B.; Mercer, Andrew A.
CS (1) Virus Research Unit, Department of Microbiology, University of Otago, P.O. Box 56, Dunedin, New Zealand: norihito.ueda@stonebow.otago.ac.nz New Zealand
SO Virology, (January 20 2003) Vol. 305, No. 2, pp. 298-309. print.
ISSN: 0042-6822.
DT Article
LA English
AB We have identified a gene encoding a homolog of vascular endothelial growth factor (VEGF) in the Pseudocowpox virus (PCPV) genome. The predicted protein shows 27% amino acid identity to human ***VEGF*** - ***A*** . It also shows 41 and 61% amino acid identity to VEGFs encoded by orf virus (ORFV) strains NZ2 and NZ7, respectively. Assays of the expressed VEGF-like protein of PCPV (PCPVVR634VEGF) demonstrated that PCPVVR634VEGF is mitogenic for endothelial cells and is capable of inducing vascular permeability. PCPVVR634VEGF bound VEGF receptor-2 (VEGFR-2) but did not bind VEGFR-1 or VEGFR-3. These results indicate that PCPVVR634VEGF is a biologically active member of the VEGF family which shares with the ORFV-encoded VEGFs a receptor binding profile that differs from those of all cellular members of the VEGF family. It seems likely that the ***biological*** ***activities*** of PCPVVR634VEGF contribute to the proliferative and highly vascularized nature of PCPV lesions.

L8 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:295399 BIOSIS
DN PREV200300295399
TI The role of moderate hypoxia in embryonic angiogenesis.
AU Nanka, Ondrej (1); Valasek, Petr; Grim, Milos
CS (1) Institute of Anatomy, Charles University First Medical Faculty, U nemocnice 3, Prague 2, Prague, CZ 128 00, Czech Republic: ondrej.nanka@lf1.cuni.cz, pvalasek@rvc.ac.uk, milos.grim@lf1.cuni.cz Czech Republic
SO FASEB Journal, (March 2003, 2003) Vol. 17, No. 4-5, pp. Abstract No. 715.8. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome San Diego, CA, USA April 11-15, 2003 FASEB . ISSN: 0892-6638.
DT Conference
LA English
AB Angiogenesis is controlled by vascular endothelial growth factors (VEGFs),

which are upregulated by hypoxia. Cells at low oxygen tension express the hypoxia induced transcription factor, HIF-1, which activates genes encoding ***VEGF*** - ***A*** and proteins that increase O2 delivery. Our aim was to correlate hypoxia with VEGF expression and blood vessel formation. Fertile quail eggs were incubated under normoxic conditions for 48 hrs and then under hypoxic conditions (16% O2) for an additional 48 or 96 hrs. Controls were incubated at normal oxygen tension. At embryonic day (ED) 4 and ED 6 embryos were injected into the vitelline vein with a marker for hypoxia, pimonidazol hydrochloride, reincubated for 1h, fixed, sectioned, and the reaction product detected with Hypoxyprobe-1 Ab. ***VEGF*** - ***A*** expression was detected by in situ hybridisation with a digoxigenin labelled riboprobe. Hypoxic regions were present even in normoxic control embryos. They became larger and stained more intensely with Hypoxyprobe-1 in hypoxic embryos. Moreover, under hypoxic conditions ***VEGF*** - ***A*** expression was elevated in Hydroxyprobe-1 positive regions, and they were surrounded by areas of increased angiogenesis as visualized with endothelial cell-specific QH-1 antibody. We conclude that moderate hypoxia is a physiological signal for embryonic blood vessel formation.

L8 ANSWER 4 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:279710 BIOSIS
DN PREV200200279710
TI Vascular endothelial growth factor C (***VEGF*** - ***C***) protein and gene, mutants thereof, and uses thereof.
AU Alitalo, Kari (1); Joukov, Vladimir
CS (1) Helsinki Finland
ASSIGNEE: Licentia Ltd, Helsinki, Finland; Ludwig Institute for Cancer Research
PI US 6361946 March 26, 2002
SO Official Gazette of the United States Patent and Trademark Office Patents, (Mar. 26, 2002) Vol. 1256, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133.
DT Patent
LA English
AB Provided are purified and isolated ***VEGF*** - ***C*** polypeptides capable of binding to at least one of KDR receptor tyrosine kinase (VEGFR-2) and Flt4 receptor tyrosine kinase (VEGFR-3); analogs of such peptides that have ***VEGF*** - ***C*** -like or VEGF-like ***biological*** ***activities*** or that are VEGF or ***VEGF*** - ***C*** inhibitors; polynucleotides encoding the polypeptides; vectors and host cells that embody the polynucleotides; pharmaceutical compositions and diagnostic reagents comprising the polypeptides; and methods of making and using the polypeptides.

L8 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:316248 BIOSIS
DN PREV200200316248
TI Relative effects of ***VEGF*** - ***A*** and ***VEGF*** - ***C*** on endothelial cell proliferation, migration, and PAF synthesis: Role of neuropilin-1.
AU Bernatchez, Pascal N.; Rollin, Simon; Soker, Shay; Sirois, Martin G. (1)
CS (1) Montreal Heart Institute (Research Center), 5000 Belanger Street, Montreal, Qc, H1T 1C8: mgsirois@icm.umontreal.ca Canada
SO Journal of Cellular Biochemistry, (2002) Vol. 85, No. 3, pp. 629-639. http://www.interscience.wiley.com/jpages/0730-2312/. print. ISSN: 0730-2312.
DT Article
LA English
AB Vascular endothelial growth factor (***VEGF*** - ***A***) is an inducer of endothelial cell (EC) proliferation, migration, and synthesis of inflammatory agents such as platelet-activating factor (PAF). Recently, neuropilin-1 (NRP-1) has been described as a coreceptor of KDR which potentiates ***VEGF*** - ***A*** activity. However, the role of NRP-1 in numerous ***VEGF*** - ***A*** activities remains unclear. To assess the contribution of NRP-1 to ***VEGF*** - ***A*** mediated EC proliferation, migration, and PAF synthesis, we used porcine aortic EC (PAEC) recombinantly expressing Flt-1, NRP-1, KDR or KDR and NRP-1. Cells were stimulated with ***VEGF*** - ***A*** , which binds to Flt-1, KDR and NRP-1, and ***VEGF*** - ***C*** , which binds to KDR only. ***VEGF*** - ***A*** was 12.4-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation in PAEC-KDR. ***VEGF*** - ***A*** and ***VEGF*** - ***C*** showed similar potency to mediate PAEC-KDR proliferation, migration, and PAF synthesis. On PAEC-KDR/NRP-1, ***VEGF*** - ***A*** was 28.6-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation and PAEC-KDR/NRP-1 proliferation (1.3-fold), migration (1.7-fold), and PAF synthesis (4.6-fold). These results suggest that cooperative binding of ***VEGF*** - ***A*** to KDR and NRP-1 enhances KDR phosphorylation and its ***biological*** ***activities*** . Similar results were obtained with bovine aortic EC that endogenously express both KDR and NRP-1 receptors. In contrast, stimulation of PAEC-Flt-1 and PAEC-NRP-1 with ***VEGF*** - ***A*** or ***VEGF*** - ***C*** did not induce proliferation, migration, or PAF synthesis. In conclusion, the presence of NRP-1 on EC preferentially increases KDR activation by ***VEGF*** - ***A*** as well as KDR-mediated ***biological*** ***activities*** , and may elicit novel intracellular events. On the other hand, ***VEGF*** - ***A*** and ***VEGF*** - ***C*** have equipotent ***biological*** ***activities*** on EC in absence of NRP-1.

L8 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:264176 BIOSIS
DN PREV200100264176
TI Comparative biological effects of VEGF and ***VEGF*** - ***C*** on endothelial cells: Role of neuropilin-1 and Flk-1/KDR receptors.
AU Bernatchez, Pascal N. (1); Soker, Shay; Rollin, Simon (1); Sirois, Martin G. (1)
CS (1) Montreal Heart Institute, 5000 Belanger St, Montreal, Qc, H1T 1C8 Canada
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1078. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN: 0892-6638.
DT Conference
LA English
SL English
AB We have recently shown that Vascular Endothelial Growth Factor (VEGF) activation of Flk-1/KDR promotes migration, proliferation and platelet-activating factor (PAF) synthesis. Neuropilin-1 (NRP1) has been described as a coreceptor of Flk-1/KDR which potentiates VEGF165 activity. However, the role of NRP1 in numerous VEGF activities remains unclear. To assess the contribution of NRP1 in VEGF-mediated EC proliferation, migration and PAF synthesis, we used porcine aortic EC (PAEC) which do not express VEGF receptors, and transfected them with KDR and/or NRP1 cDNA. A preliminary study showed that unlike VEGF, ***VEGF*** - ***C*** does not bind to NRP-1. In the present study, we compare the biological effects of VEGF and ***VEGF*** - ***C*** in EC. First, we observed that VEGF was 2.7-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation in PAEC-KDR. However, VEGF and ***VEGF*** - ***C*** showed similar potency to mediate PAEC-KDR proliferation, migration and PAF synthesis. This suggests that maximal phosphorylation of KDR is above the optimal activation required for its maximal ***biological*** ***activities*** . On PAEC-KDR-NRP1, VEGF was 6.6-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation. In addition, VEGF was more potent than ***VEGF*** - ***C*** in eliciting PAEC-KDR-NRP1 proliferation (1.33-fold), migration (1.73-fold) and PAF synthesis (3.60-fold). This suggests that cooperative binding of VEGF to KDR and NRP1 enhances KDR phosphorylation and subsequently proliferation, migration and PAF synthesis. Stimulation of PAEC-NRP1 with VEGF or ***VEGF*** - ***C*** did not induce the activities described above. In conclusion, VEGF and ***VEGF*** - ***C*** have equipotent ***biological*** ***activities*** in the absence of NRP1. Cooperative binding of VEGF to NRP1 and KDR potentiated VEGF-mediated activity compared with ***VEGF*** - ***C*** . These results suggest that the presence of NRP1 on EC might increase or sustain the response upon KDR activation.

L8 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2002:238646 BIOSIS
DN PREV200200238646
TI Soluble VEGFR-1 secreted by endothelial cells and monocytes is present in human serum and plasma from healthy donors.
AU Barleon, Bernhard (1); Reusch, Petra; Totzke, Frank; Herzog, Christel; Keck, Christoph; Martiny-Baron, Georg; Marme, Dieter
CS (1) RELIATech GmbH, Mascheroderweg 1b, D-38124, Braunschweig: Bernhard.Barleon@reliatech.de Germany
SO Angiogenesis, (2001) Vol. 4, No. 2, pp. 143-154. http://www.kluweronline.com/issn/0969-6970. print. ISSN: 0969-6970.
DT Article
LA English
AB It was shown before that the soluble form of VEGFR-1 (sVEGFR-1) is present in serum of pregnant women. The aim of the present study was to investigate the presence of this endogenous vascular endothelial growth factor-A (***VEGF*** - ***A***) antagonist in human serum in more detail. sVEGFR-1 was detected in human serum and plasma from normal healthy male and female donors by ELISA. sVEGFR-1 levels ranged from non-detectable up to 440 pg/ml, with no significant difference between male and female donors. In addition, vein endothelial cells (ECs) from an intact vascular bed, the umbilical cord, were shown to secrete sVEGFR-1. Furthermore, human peripheral blood monocytes, a non-EC type expressing VEGFR-1, were shown to contribute to the sVEGFR-1 detectable in human serum and plasma for the first time. EC- and monocyte-derived sVEGFR-1 proved capable of inhibiting the VEGF-induced proliferation and migration of ECs in vitro. Finally, secretion of sVEGFR-1 was increased by the angiogenic factor basic fibroblast growth factor (bFGF) in human ECs and was also enhanced in lipopolysaccharide-activated human monocytes. In human umbilical vein endothelial cells, both the membrane-bound and the sVEGFR-1 seem to be equally regulated on the mRNA as well as the protein level. The presence of an sVEGFR-1 in human serum and plasma of normal male and female donors strongly suggests that it plays an important role as a naturally occurring VEGF antagonist in the regulation and availability of VEGF-mediated ***biological*** ***activities*** in vivo.

L8 ANSWER 8 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4

AN 2001:385230 BIOSIS
DN PREV200100385230
TI Alternative splicing of the human VEGFGR-3/FLT4 gene as a consequence of an integrated human endogenous retrovirus.
AU Hughes, David C. (1)
CS (1) Reproductive Biology and Genetics Group, Division of Medicine, University of Birmingham, Birmingham, B15 2TT: d.c.hughes@bham.ac.uk UK
SO Journal of Molecular Evolution, (August, 2001) Vol. 53, No. 2, pp. 77-79. print.
ISSN: 0022-2844.
DT Article
LA English
SL English
AB The vascular endothelial growth factor receptor 3 (VEGFR-3/FLT4) is a receptor tyrosine kinase that regulates angiogenesis and vasculogenesis in response to the binding of the ligands ***VEGF*** - ***C*** and VEGF-D. Mutations in VEGFR-3 have been identified in patients with primary lymphoedema. It has been noted previously that whilst in the mouse there is only a single Vegfr-3 transcript, in humans there are two transcripts of 5.8 and 4.5 kb, of which the shorter encodes a protein that lacks the C-terminal 65 amino acids. These two isoforms also differ in their ***biological*** ***activity*** . Analysis of the human VEGFR-3 cDNA and genomic sequence reveals that these two isoforms arise by alternative splicing of the terminal exons. The shorter transcript is generated by splicing into the long terminal repeat of a human endogenous retrovirus located between the last two exons, thus explaining the lack of the shorter transcript in the mouse. The retention of the retroviral sequences in the FLT4 locus suggests that this retrotransposition event has contributed significant additional function to this gene. This provides support for a role for integrated retroviruses in modulating gene activity and participating in evolutionary processes.

L8 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 1999:495026 BIOSIS
DN PREV199900495026
TI Effect of novel CAAX peptidomimetic farnesyltransferase inhibitor on angiogenesis in vitro and in vivo.
AU Gu, W.-Z.; Tahir, S. K.; Wang, Y.-C.; Zhang, H.-C.; Cherian, S. P.; O'Connor, S.; Leal, J. A.; Rosenberg, S. H.; Ng, S.-C. (1)
CS (1) Cancer Research, Pharmaceutical Product Research Division, Department 4N6 AP9/2, Abbott Laboratories, Abbott Park, IL USA
SO European Journal of Cancer, (Sept., 1999) Vol. 35, No. 9, pp. 1394-1401. ISSN: 0959-8049.
DT Article
LA English
SL English
AB Ras oncogenes can contribute to tumour development by stimulating vascular endothelial growth factor (VEGF)-dependent angiogenesis. The effect of Ras on angiogenesis may be affected by farnesyltransferase inhibitors (FTI) since farnesylation of Ras is required for its ***biological*** ***activity*** . In this paper we evaluated the effect of A-170634, a novel and potent CAAX FTI on angiogenesis. Human umbilical vein endothelial cell (HUVEC) tube formation and VEGF secretion were used to assess the effect of A-170634 on angiogenesis in vitro. In vivo, nude mice were injected with the K-ras mutant colon carcinoma cell line HCT116 and treated subcutaneously with A-170634 using osmotic minipump infusion for 10 days. The effect of A-170634 on corneal angiogenesis in vivo was assessed using pellets containing hydron, ***VEGF*** , ***A*** -170634 or vehicle. In vitro, A-170634 selectively inhibited farnesyltransferase activity over the closely related geranylgeranyltransferase I, inhibited Ras processing, blocked anchorage-dependent and -independent growth of HCT116 K-ras mutated cells, decreased HUVEC capillary structure formation, decreased VEGF secretion from tumour cells and HUVEC growth stimulating activity in a dose-dependent manner. In vivo, tumour growth was decreased by 30% and vascularisation in and around the tumours was reduced by 41% following drug-treatment with no apparent toxicity to the animals. VEGF-induced corneal neovascularisation was reduced by 80% following A-170634 treatment for 7 days. The data presented here demonstrated that A-170634 was a potent and selective peptidomimetic CAAX FTI with anti-angiogenic properties. These results implied that A-170634 may affect tumour growth in vivo by one or more antitumour pathways.

L8 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 2000:69739 BIOSIS
DN PREV200000069739
TI Lymphangiogenesis and ***biological*** ***activity*** of vascular endothelial growth factor (***VEGF***)- ***C*** .
AU Mandriota, Stefano J. (1); Pepper, Michael S. (1)
CS (1) Departement de Morphologie, Centre Medical Universitaire, 1, rue Michel Servet, 1211, Geneve, 4 Switzerland
SO Journal de la Societe de Biologie, (1999) Vol. 193, No. 2, pp. 159-163. ISSN: 1295-0661.
DT Article
LA French
SL English; French
AB Vascular endothelial growth factor (***VEGF***)- ***C*** is a new member of the VEGF family, a group of polypeptide growth factors which play key roles in the physiology and pathology of many aspects of the cardiovascular system, including vasculogenesis, hematopoiesis, angiogenesis and vascular permeability. VEGF signaling in endothelial cells occurs through three tyrosine kinase receptors (VEGFRs), expressed by endothelial cells and hematopoietic precursors. With respect to the first VEGF described, ***VEGF*** - ***A*** , which is an endothelial cell specific mitogen and key angiogenic factor, ***VEGF*** - ***C*** seems to play a major role in the development of the lymphatic system. This may reflect the different binding properties of VEGFs to VEGFRs, in that ***VEGF*** - ***A*** binds to VEGFR-1 and -2, whereas ***VEGF*** - ***C*** acts through VEGFR-3, whose expression becomes restricted to lymphatics and certain veins during development. However, the finding that ***VEGF*** - ***C*** also binds to and activates VEGFR-2 may explain why it induces angiogenesis under certain conditions, which makes it relevant to experimental or clinical settings in which one would wish to block or to stimulate angiogenesis. In this paper we briefly discuss current knowledge on the ***biological*** ***activity*** of ***VEGF*** - ***C*** , emphasizing that, as has already been shown for a number of other angiogenic factors, the biological effects of ***VEGF*** - ***C*** are strictly dependent on the activity of other angiogenic regulators present in the microenvironment of the responding endothelial cells.

=> s phVEGF165
L9 71 PHVEGF165

=> s phvegf2
L10 3 PHVEGF2

=> s l9 or l10
L11 74 L9 OR L10

=> s l11 and biological activ?
L12 0 L11 AND BIOLOGICAL ACTIV?

=> dup rem l11
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L13 44 DUP REM L11 (30 DUPLICATES REMOVED)

=> s l13 and py<=2000
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L14 30 L13 AND PY<=2000

=> s l14 and HUVAC
L15 0 L14 AND HUVAC

=> s l14 and HUVeC
L16 0 L14 AND HUVEC

=> d bib abs l14

L14 ANSWER 1 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:452689 BIOSIS
DN PREV200000452689
TI Highly efficient cell-mediated gene transfer using non-viral vectors and FuGeneTM6: In vitro and in vivo studies.
AU Hellgren, I. (1); Drvota, V.; Pieper, R.; Enoksson, S.; Blomberg, P.; Islam, K. B.; Sylven, C.
CS (1) Department of Cardiology, The Clinical Research Center, Novum, Huddinge, 5th floor, 141 86, Stockholm Sweden
SO CMLS Cellular and Molecular Life Sciences, (***August, 2000***) Vol. 57, No. 8-9, pp. 1326-1333. print.
ISSN: 1420-682X.
DT Article
LA English
SL English
AB The present study was undertaken to develop an efficient non-viral gene delivery system for cardiovascular gene therapy. We investigated transfection efficiency and toxic properties of the new transfection reagent, FuGeneTM6, and compared it with two other transfection reagents, TfxTM-50 and LipoTaxiTM. For in vivo experiments, the plasmid was delivered intramuscularly via transplantation of fibroblasts transfected with plasmid and FuGeneTM6. Conditions for efficient gene delivery were initially studied in vitro. Human and rabbit fibroblasts were isolated from skin, cultured and transfected with ***phVEGF165*** or pCMVbeta gal plasmids, coding for vascular endothelial growth factor (VEGF) or beta-galactosidase, respectively. The effect of the DNA amount in the DNA:transfection reagent ratio on plasmid uptake were studied. Of the transfection reagents tested, only FuGeneTM6 provided high-efficiency and dose-dependent plasmid transfer both for cell-localised (beta-galactosidase) and secreted (VEGF) gene products. When analysed with an MTT assay, FuGeneTM6 showed no toxicity at low doses. Optimised conditions were applied for in vivo reporter gene delivery. Rabbits were injected intramuscularly with ex vivo-transfected fibroblasts. As in in vitro studies, ex vivo-transfected fibroblasts showed highly efficient gene expression in vivo. Tissue sections were analysed with macrophage-specific immunostaining. No signs of inflammation were seen in the region of fibroblast injection. This study demonstrates that FuGeneTM6 is a highly efficient transfection reagent that may be useful for in vitro non-viral transfection of primary human and rabbit fibroblasts and for in vivo therapeutic non-viral gene delivery.

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L16 HAS NO ANSWERS
'2- ' IS NOT A VALID SEARCH STATUS KEYWORD
Search status keywords:
NONE --- Display only the number of postings.
STATUS -- Display statistics of the search.
ENTER SEARCH STATUS OPTION (NONE), STATUS, OR ?:none
L9 71 SEA PHVEGF165
L10 3 SEA PHVEGF2
L11 74 SEA L9 OR L10
L13 44 DUP REM L11 (30 DUPLICATES REMOVED)
L14 30 SEA L13 AND PY<=2000
L16 0 SEA L14 AND HUVEC

=> d bib abs l14 2-
YOU HAVE REQUESTED DATA FROM 29 ANSWERS - CONTINUE? Y/(N):y

L14 ANSWER 2 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:422248 BIOSIS
DN PREV200000422248
TI Signs of bioactivity for gene therapy with ***phVEGF165*** in end-stage ischemic heart disease.
AU Sarkar, N. (1); Drvota, V. (1); Y.-Hassan, S. (1); Nygren, A. (1); Brodin, L. A. (1); Blomberg, P. (1); vd Linden, J. (1); Lindblom, D. (1); Islam, K. (1); Sylven, C. (1)
CS (1) Huddinge University Hospital, Stockholm Sweden
SO Journal of Vascular Research, (***May, 2000***) Vol. 37, No. Suppl. 1, pp. 13. print.
Meeting Info.: 21st European Conference on Microcirculation Stockholm, Sweden June 04-07, 2000 European Society for Microcirculation
. ISSN: 1018-1172.
DT Conference
LA English
SL English

L14 ANSWER 3 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:422176 BIOSIS
DN PREV200000422176
TI Left ventricular electromechanical mapping to assess efficacy of ***phVEGF165*** gene transfer for therapeutic angiogenesis in chronic myocardial ischemia.
AU Vale, Peter R.; Losordo, Douglas W. (1); Milliken, Charles E.; Maysky, Michael; Esakof, Darryl D.; Symes, James F.; Isner, Jeffrey M.
CS (1) St. Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135 USA
SO Circulation, (***August 29, 2000***) Vol. 102, No. 9, pp. 965-974. print.
ISSN: 0009-7322.
DT Article
LA English
SL English
AB Background: NOGA left ventricular (LV) electromechanical mapping (EMM) can
be used to distinguish among infarcted, ischemic, and normal myocardium. We investigated the use of percutaneous LV EMM to assess the efficacy of myocardial gene transfer (GTx) of naked plasmid DNA encoding for vascular endothelial growth factor (***phVEGF165***), administered during surgery by direct myocardial injection in patients with chronic myocardial ischemia. Methods and Results: A total of 13 consecutive patients (8 men, mean age 60.1+-2.3 years) with chronic stable angina due to angiographically documented coronary artery disease, all of whom had failed conventional therapy (drugs, PTCA, and/or CABG), were treated with direct myocardial injection of ***phVEGF165*** via a minithoracotomy. Foci of ischemic myocardium were identified on LV EMM by preserved viability associated with an impairment in linear local shortening. Myocardial viability, defined by mean unipolar and bipolar voltage recordings gtoreq5 and gtoreq2 mV, respectively, did not change significantly after GTx. Analysis of linear local shortening in areas of myocardial ischemia, however, disclosed significant improvement after (15.26+-0.98%) versus before (9.94+-1.53%, P=0.004) ***phVEGF165*** GTx. The area of ischemic myocardium was consequently reduced from 6.45+-1.37 cm2 before GTx to 0.95+-0.41 cm2 after GTx (P=0.001). These findings corresponded to improved perfusion scores calculated from single-photon emission CT-sestamibi myocardial perfusion scans recorded at rest (7.4+-2.1 before GTx versus 4.5+-1.4 after GTx, P=0.009) and after pharmacological stress (12.8+-2.7 before GTx versus 8.5+-1.7 after GTx, P=0.047). Conclusions: The results of EMM constitute objective evidence that ***phVEGF165*** GTx augments perfusion of ischemic myocardium. These findings, together with reduction in the size of the defects documented at rest by serial single-photon emission CT-sestamibi imaging, suggest that ***phVEGF165*** GTx may successfully rescue foci of hibernating myocardium.

L14 ANSWER 4 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:415928 BIOSIS
DN PREV200000415928
TI Dose-response transfection and vascular effects of vascular endothelial growth factor165 (***phVEGF165***) in normoxic and hypoxic rat myocardium.
AU Sarkar, N. (1); Wardell, E.; Jamsa, A.; Drovta, V.; Sylven, C.
CS (1) Huddinge University Hospital, Stockholm Sweden
SO Journal of Vascular Research, (***May, 2000***) Vol. 37, No. Suppl. 1, pp. 61. print.
Meeting Info.: 21st European Conference on Microcirculation Stockholm, Sweden June 04-07, 2000 European Society for Microcirculation
. ISSN: 1018-1172.
DT Conference
LA English
SL English

L14 ANSWER 5 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:191077 BIOSIS
DN PREV200000191077
TI Evaluation of the effects of intramyocardial injection of DNA expressing vascular endothelial growth factor (VEGF) in a myocardial infarction model in the rat: Angiogenesis and angioma formation.
AU Schwarz, Ernst R.; Speakman, Mark T.; Patterson, Mike; Hale, Sharon S.; Isner, Jeffrey M.; Kedes, Laurence H.; Kloner, Robert A. (1)
CS (1) Division of Cardiology, Heart Institute, Good Samaritan Hospital, University of Southern California, 1225 Wilshire Boulevard, Los Angeles, CA, 90017-2395 USA
SO Journal of the American College of Cardiology, (***April, 2000***) Vol. 35, No. 5, pp. 1323-1330.
ISSN: 0735-1097.
DT Article
LA English
SL English
AB OBJECTIVES: The effects of direct intramyocardial injection of the plasmid encoding vascular endothelial growth factor (***phVEGF165***) in the border zone of myocardial infarct tissue in rat hearts were investigated. BACKGROUND: Controversy exists concerning the ability of VEGF to induce angiogenesis and enhance coronary flow in the myocardium. METHODS: Sprague-Dawley rats received a ligation of the left coronary artery to induce myocardial infarction (MI). At 33.1 +- 6.5 days, the rats were injected with ***phVEGF165*** at one location and control plasmid at a second location (500 mug DNA, n = 24) or saline (n = 16). After 33.1 +- 5.7 days, the hearts were excised for macroscopic and histologic analysis. Regional blood flow ratios were measured in 18 rats by radioactive microspheres. RESULTS: ***phVEGF165*** -treated sites showed macroscopic angioma-like structures at the injection site while control DNA and saline injection sites did not. By histology, 21/24 ***phVEGF165*** -treated hearts showed increased focal epicardial blood vessel density and angioma-like formation. Quantitative morphometric evaluation in 20 ***phVEGF165*** -treated hearts revealed 44.4 +- 10.5 vascular structures per field in phVFGF165-treated hearts versus 21.4 +- 4.7 in control DNA injection sites ($p < 0.05$). Regional myocardial blood flow ratios between the injection site and noninfarcted area did not demonstrate any difference between ***phvEGF165*** -treated hearts (0.9 +- 0.2) and saline-treated hearts (0.7 +- 0.1). CONCLUSIONS: Injection of DNA for VEGF in the border zone of MI in rat hearts induced angiogenesis. Angioma formation at the injection sites did not appear to contribute to regional myocardial blood flow, which may be a limitation of gene therapy for this application.

L14 ANSWER 6 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:75787 BIOSIS
DN PREV200000075787
TI Intramyocardial gene therapy with naked DNA encoding vascular endothelial growth factor improves collateral flow to ischemic myocardium.
AU Tio, Rene A.; Tkebuchava, Tengis; Scheuermann, Thomas H.; Lebherz, Corinna; Magner, Meredith; Kearny, Marianne; Esakof, Daryll D.; Isner, Jeffrey M.; Symes, James F. (1)
CS (1) 11 Nevins Street, Suite 306, Boston, MA USA
SO Human Gene Therapy, (***Dec. 10, 1999***) Vol. 10, No. 18, pp. 2953-2960.
ISSN: 1043-0342.
DT Article
LA English
SL English
AB Both VEGF protein and VEGF DNA in combination with an adenoviral vector have been shown to enhance collateral formation in a porcine model of chronic myocardial ischemia. We sought to determine whether direct intramyocardial injection of naked DNA encoding for VEGF could similarly improve myocardial perfusion. Initially, 23 nonischemic pigs received either 200 mug of plasmid DNA encoding beta-galactosidase (pCMVbeta, n = 11) or 500 mug of ***phVEGF165*** (n = 12) into four separate sites in the myocardium via a small anterolateral thoracotomy incision in the fourth intercostal space. Two additional groups of pigs received an intramyocardial injection of either ***phVEGF165*** (n = 6) or pCMVbeta (n = 7) 3 to 4 weeks after implantation of an ameroid constrictor around the left circumflex coronary artery. The injections caused no change in heart rate or blood pressure, and no ventricular arrhythmias or histologic evidence of inflammation. VEGF protein was detected by Western blot in VEGF-treated animals, with the strongest bands closest to the injection site. Plasma VEGF concentration (ELISA) increased from 3 +- 2 to 27 +- 13 pg/ml (p = 0.035) by day 4 after treatment. No increase in VEGF protein was noted in pCMVbeta-treated animals whereas these did stain positive for beta-Gal. Resting myocardial blood flow (colored microspheres) was significantly reduced in the ischemic versus nonischemic

territory in control animals (1.07 +- 0.05 versus 1.32 +- 0.05; p < 0.05) but not VEGF-treated pigs (1.32 +- 0.24 versus 1.13 +- 0.12; p = NS). Maximal vasodilatation with adenosine significantly increased flow to the ischemic region in VEGF-treated pigs (2.16 +- 0.57 versus 1.32 +- 0.24; p < 0.05) but not controls (1.31 +- 0.05 versus 1.17 +- 0.06; p = NS). Collateral filling of the occluded circumflex artery improved in five of six VEGF-treated pigs (mean change in Rentrop score, +1.5). We conclude that direct intramyocardial transfection ***phVEGF165*** is safe and capable of producing sufficient VEGF protein to enhance collateral formation and myocardial perfusion. This approach may offer an alternative therapy for patients with intractable myocardial ischemia not amenable to PTCA or CABG.

L14 ANSWER 7 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:17784 BIOSIS
DN PREV200000017784
TI Direct myocardial injection of ***phVEGF165*** : Results of complete patient cohort in phase 1/2 clinical trial.
AU Vale, Peter R. (1); Losordo, Douglas W. (1); Dunnington, Cheryl H. (1); Esakof, Daryl D. (1); Maysky, Michael (1); Milliken, Charles E. (1); Lathi, Kishor (1); Symes, James F. (1)
CS (1) St Elizabeth's Med Ctr, Boston, MA USA
SO Circulation, (***Nov. 2, 1999***) Vol. 110, No. 18 SUPPL., pp. I.477.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999
ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 8 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:17594 BIOSIS
DN PREV200000017594
TI Age<50 years and rest pain predict positive clinical outcome after intramuscular gene transfer of ***phVEGF165*** in 55 patients with critical limb ischemia.
AU Rauh, Guenter (1); Gravereaux, Edwin (1); Pieczek, Ann (1); Radley, Stephanie (1); Schainfeld, Robert (1); Isner, Jeffrey M. (1)
CS (1) St Elizabeth's Med Ctr, Boston, MA USA
SO Circulation, (***Nov. 2, 1999***) Vol. 110, No. 18 SUPPL., pp. I.319.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999
ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 9 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:523474 BIOSIS
DN PREV199900523474
TI Naked DNA encoding and hypoxia-inducible factor 1alpha (HIF-1alpha)/VP16 hybrid transcription factor enhances angiogenesis in rabbit hindlimb ischemia: An alternate method for therapeutic angiogenesis utilizaing a transcriptional regulatory system.
AU Shyu, Kou-Gi (1); Vincent, Karen A.; Luo, Yuxia; Magner, Meredith; Tio, Rene A.; Jiang, Canwen; Akita, Geoffrey Y.; Isner, Jeffrey M.; Gregory, Richard J.
CS (1) St. Elizabeth's Med. Cent., Boston, MA USA
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I68.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association . ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 10 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:513991 BIOSIS
DN PREV199900513991
TI Treatment of Buerger's disease by intramuscular gene transfer of ***phVEGF165*** .
AU Rauh, Guenter; Baumgartner, Iris; Pieczek, Ann; Blair, Richard; Symes, James; Isner, Jeffrey M.
CS St. Elizabeth's Med. Cent., Boston, MA USA
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I66.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association . ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 11 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:513896 BIOSIS
DN PREV199900513896
TI Patency of dorsalis pedis artery as a predictor of clinical outcome after intramuscular gene transfer of ***phVEGF165*** in patients with non-healing ischemic ulcers.
AU Isner, Jeffrey M.; Blair, Richard; Vale, Peter; Schainfeld, Robert M.
CS St. Elizabeth's Med. Cent., Boston, MA USA
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I13.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association . ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 12 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:508839 BIOSIS
DN PREV199900508839
TI Arterial gene therapy for inhibiting restenosis in patients with claudication undergoing superficial femoral artery angioplasty.
AU Vale, Peter R. (1); Wuensch, Debra I.; Rauh, Guenter F.; Rosenfield, Kenneth M.; Schainfeld, Robert M.; Isner, Jeffrey M.
CS (1) St. Elizabeth's Med. Cent., Boston, MA USA
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I66.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association . ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 13 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:413483 BIOSIS
DN PREV199900413483
TI Gene therapy for myocardial angiogenesis.
AU Losordo, Douglas W. (1); Vale, Peter R.; Isner, Jeffrey M.
CS (1) Department of Medicine, Division of Cardiovascular Research, St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135 USA
SO American Heart Journal, (***Aug., 1999***) Vol. 138, No. 2 PART 2, pp. S132-S141.
ISSN: 0002-8703.
DT General Review
LA English
SL English
AB In patients in whom antianginal medications fail to provide sufficient symptomatic relief, additional interventions such as angioplasty or bypass surgery may be required. Although both types of intervention have been shown to be effective for various types of patients, a certain group of patients may not be candidates for either intervention because of the diffuse nature of their coronary artery disease. Moreover, there are many patients in whom recurrent narrowing and/or occlusion of bypass conduits after initially successful surgery has left the patient again symptomatic with no further angioplasty or surgical option. Ischemic muscle represents a promising target for gene therapy with naked plasmid DNA. Intramuscular transfection of genes encoding angiogenic cytokines, particularly those naturally secreted by intact cells, may constitute an alternative treatment strategy for patients with extensive tissue ischemia in whom contemporary therapies (antianginal medications, angioplasty,bypass surgery) have previously failed or are not feasible. This strategy is designed to promote the development of supplemental collateral blood vessels that will constitute endogenous bypass conduits around occluded native arteries, a strategy termed "therapeutic angiogenesis." Preclinical animal studies from our laboratory have established that intramuscular gene transfer may be used to successfully accomplish therapeutic angiogenesis. More recently, phase 1 clinical studies from our institution have established that intramuscular gene transfer may be used to safely and successfully accomplish therapeutic angiogenesis in patients with critical limb ischemia. The notion that this concept could be extrapolated to the treatment of chronic myocardial ischemia was demonstrated in our laboratory by administering recombinant human vascular endothelial growth factor (VEGF) to a porcine model of chronic myocardial ischemia. Recent experiments performed in this same porcine model of myocardial ischemia have shown that direct intramyocardial gene transfer of naked plasmid DNA encoding VEGF (***phVEGF165*** , the identical plasmid used in our previous animal and human clinical trials) can be safely and successfully achieved through a minimally invasive chest wall incision. Finally, initial results have supported the concept that intramyocardial injection of naked plasmid DNA encoding VEGF can achieve therapeutic angiogenesis, as demonstrated by clinical improvement in patient symptoms and improved myocardial perfusion shown by single-photon emission computed tomography-sestamibi imaging.

L14 ANSWER 14 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:61069 BIOSIS
DN PREV199900061069
TI Gene therapy for myocardial angiogenesis: Initial clinical results with direct myocardial injection of phVEFG165 as sole therapy for myocardial ischemia.
AU Losordo, Douglas W.; Vale, Peter R.; Symes, James F.; Dunnington, Cheryl H.; Esakof, Darryl D.; Maysky, Michael; Ashare, Alan B.; Lathi, Kishor; Isner, Jeffrey M. (1)
CS (1) St. Elizabeth's Medical Center, 736 Cambridge St., Boston, MA 02135 USA
SO Circulation, (***Dec. 22-29, 1998***) Vol. 98, No. 25, pp. 2800-2804.
ISSN: 0009-7322.
DT Article
LA English
AB Background- We initiated a phase I clinical study to determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (VEGF) as sole therapy for patients with symptomatic myocardial ischemia. Methods and Results- VEGF gene transfer (GTx) was

performed in 5 patients (all male, ages 53 to 71) who had failed conventional therapy; these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding VEGF (***phVEGF165***) was injected directly into the ischemic myocardium via a mini left anterior thoracotomy. Injections caused no changes in heart rate (pre-GTx = 75 +- 15/min versus post-GTx = 80 +- 16/min, P=NS), systolic BP (114+-7 versus 118+-7 mm Hg, P=NS), or diastolic BP (57+-2 versus 59+-2 mmHg, P=NS). Ventricular arrhythmias were limited to single unifocal premature beats at the moment of injection. Serial ECGs showed no evidence of new myocardial infarction in any patient. Intraoperative blood loss was 0 to 50 cm3, and total chest tube drainage was 110 to 395 cm3. Postoperative cardiac output fell transiently but increased within 24 hours (preanesthesia=4.8 +- 0.4 versus postanesthesia=4.1 +- 0.3 versus 24 hours postoperative=6.3 +- 0.8, P=0.02). Time to extubation after closure was 18.4 +- 1.4 minutes; average postoperative hospital stay was 3.8 days. All patients had significant reduction in angina (nitroglycerin (NTG) use=53.9 +- 10.0/wk pre-GTx versus 9.8 +- 6.9/wk post-GTx, P<0.03). Postoperative left ventricular ejection fraction (LVEF) was either unchanged (n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced ischemia was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients. Coronary angiography showed improved Rentrop score in 5 of 5 patients. Conclusions- This initial experience with naked gene transfer as sole therapy for myocardial ischemia suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall incision, is safe and may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial ischemia.

L14 ANSWER 15 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:61029 BIOSIS
DN PREV199900061029
TI Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: Preliminary clinical results.
AU Isner, Jeffrey M.; Baumgartner, Iris; Rauh, Guenter; Schainfeld, Robert; Blair, Richard; Manor, Orit; Razvi, Syed; Symes, James F. (1)
CS (1) St. Elizabeth's Med. Cent., 11 Nevins St., Ste. 306, Boston, MA 02135 USA
SO Journal of Vascular Surgery, (***Dec., 1998***) Vol. 28, No. 6, pp. 964-975.
ISSN: 0741-5214.
DT Article
LA English
AB Purpose: Thromboangiitis obliterans (TAO), or Buerger's disease, a distinct form of vascular occlusive disease that afflicts the peripheral arteries of young smokers, is often characterized by an inexorable downhill course even in patients who discontinue smoking once a stage of critical limb ischemia associated with ulceration or gangrene is reached. As part of a phase I clinical trial to document the safety and efficacy of intramuscular gene transfer of naked plasmid DNA-encoding vascular endothelial growth factor (***phVEGF165***) in the treatment of critical limb ischemia, we treated TAO in 6 patients. Methods: Seven limbs in 6 patients (3 men, 3 women; mean age, 33 years; range, 33 to 51 years) who satisfied the criteria for TAO and had signs or symptoms of critical limb ischemia were treated twice, 4 weeks apart, with 2 or 4 mg of ***phVEGF165*** , which was administered by direct intramuscular injection at 4 arbitrarily selected sites in the ischemic limb. The gene expression was documented by enzyme-linked immunosorbent assay that was performed on peripheral blood samples. Results: The ulcers that were nonhealing for more than 1 month healed completely in 3 of 5 limbs after the intramuscular ***phVEGF165*** gene therapy. Nocturnal rest pain was relieved in the remaining 2 patients, although both continue to have claudication. The evidence of the improved perfusion to the distal ischemic limb included an increase of more than 0.1 in the ankle brachial index in 3 limbs, an improved flow shown with magnetic resonance imaging in 7 of the 7 limbs, and newly visible collateral vessels shown with serial contrast angiography in 7 of the 7 limbs. The adverse consequences of the ***phVEGF165*** gene transfer were limited to transient ankle or calf edema in 3 of the 7 limbs. Two patients with advanced distal forefoot gangrene ultimately required below-knee amputation despite the evidence of improved perfusion. A histologic section disclosed the classic pathologic findings of TAO. Conclusion: Therapeutic angiogenesis with ***phVEGF165*** gene transfer, if instituted before the development of forefoot gangrene, may provide a novel therapy for patients with advanced Buerger's disease that is unresponsive to standard medical or surgical treatment methods.

L14 ANSWER 16 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:207109 BIOSIS
DN PREV199800207109
TI Constitutive expression of ***phVEGF165*** after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia.
AU Baumgartner, Iris; Pieczek, Ann; Manor, Orit; Blair, Richard; Kearney, Marianne; Walsh, Kenneth; Isner, Jeffrey M. (1)
CS (1) St. Elizabeth's Med. Cent. Boston, 736 Cambridge St., Boston, MA 02135 USA
SO Circulation, (***March 31, 1998***) Vol. 97, No. 12, pp. 1114-1123.
ISSN: 0009-7322.
DT Article
LA English
AB Background-Preclinical studies have indicated that angiogenic growth factors can stimulate the development of collateral arteries, a concept called "therapeutic angiogenesis." The objectives of this phase I clinical trial were (1) to document the safety and feasibility of intramuscular gene transfer by use of naked plasmid DNA encoding an endothelial cell mitogen and (2) to analyze potential therapeutic benefits in patients with critical limb ischemia. Methods and Results-Gene transfer was performed in 10 limbs of 9 patients with nonhealing ischemic ulcers (n=7/10) and/or rest pain (n= 10/10) due to peripheral arterial disease. A total dose of 4000 mug of naked plasmid DNA encoding the 165-amino-acid isoform of human vascular endothelial growth factor (***phVEGF165***) was injected directly into the muscles of the ischemic limb. Gene expression was documented by a transient increase in serum levels of VEGF monitored by ELISA. The ankle-brachial index improved significantly (0.33+-0.05 to 0.48+-0.03, P=.02); newly visible collateral blood vessels were directly documented by contrast angiography in 7 limbs; and magnetic resonance angiography showed qualitative evidence of improved distal flow in 8 limbs. Ischemic ulcers healed or markedly improved in 4 of 7 limbs, including successful limb salvage in 3 patients recommended for below-knee amputation. Tissue specimens obtained from an amputee 10 weeks after gene therapy showed foci of proliferating endothelial cells by immunohistochemistry. PCR and Southern blot analyses indicated persistence of small amounts of plasmid DNA. Complications were limited to transient lower-extremity edema in 6 patients, consistent with VEGF enhancement of vascular permeability. Conclusions-These findings may be cautiously interpreted to indicate that intramuscular injection of naked plasmid DNA achieves constitutive overexpression of VEGF sufficient to induce therapeutic angiogenesis in selected patients with critical limb ischemia.

L14 ANSWER 17 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:15353 BIOSIS
DN PREV199800015353
TI Evidence of therapeutic angiogenesis in patients with critical limb ischemia after intramuscular ***phVEGF165*** gene transfer.
AU Baumgartner, Iris; Pieczek, Ann M.; Blair, Richard; Manor, Orit; Walsh, Kenneth; Isner, Jeffrey M.
CS St. Elizabeth's Med. Cent., Boston, MA USA
SO Circulation, (***10/21/97, 1997***) Vol. 96, No. 8 SUPPL., pp. I32.
Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 18 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:15147 BIOSIS
DN PREV199800015147
TI Evidence of therapeutic angiogenesis in patients with critical limb ischemia after intramuscular ***phVEGF165*** gene transfer.
AU Baumgartner, Iris; Pieczek, Ann M.; Blair, Richard; Manor, Orit; Walsh, Kenneth; Isner, Jeffrey M.
CS St. Elizabeth's Med. Cent., Boston, MA USA
SO Circulation, (***10/21/97, 1997***) Vol. 96, No. 8 SUPPL., pp. IH.
Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322.
DT Conference
LA English

L14 ANSWER 19 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:1860 BIOSIS
DN PREV199800001860
TI Treatment of acute limb ischemia by intramuscular injection of vascular endothelial growth factor gene.
AU Tsurumi, Yukio; Kearney, Marianne; Chen, Dongfen; Silver, Marcy; Takeshita, Satoshi; Yang, Jihong; Symes, James F.; Isner, Jeffrey M. (1)
CS (1) St. Elizabeth's Med. Cent. Boston, 736 Cambridge St., Boston, MA 02135 USA
SO Circulation, (***Nov. 4, 1997***) Vol. 96, No. 9 SUPPL., pp. II382-II388.
ISSN: 0009-7322.
DT Article
LA English
AB Background: Ischemic skeletal muscle has been shown to be advantageous for taking up and expressing genes transferred in the form of naked plasmid DNA. Therefore, acutely ischemic skeletal muscle may represent a potential target for IM gene therapy with naked DNA. Accordingly, we investigated the impact of IM injection of plasmid DNA encoding the secreted angiogenic growth factor, vascular endothelial growth factor (VEGF), on collateral vessel development in an animal model of acute hindlimb ischemia. Methods and Results: After ligation of distal external iliac artery in New Zealand White rabbits, we directly injected 500mug of ***phVEGF165*** into the ischemic thigh muscles. At 30 days posttransfection, VEGF-transfected animals had more angiographically recognizable collateral vessels (angiographic score=0.72+-0.06 versus 0.48+-0.10; P<.01) as well as histologically assessed capillaries (248 +- 37 versus 180 +- 32/mm2 p<.01) compared to controls. Hemodynamic deficit was less severe in VEGF-transfected animals by calf systolic blood pressure ratio (0.80+-0.09

versus 0.56+-0.10, P<.01) and by flow to the ischemic limb measured with Doppler guidewire (resting flow=22+-5 versus 14+-4; P<.01; hyperemic flow=59+-17 versus 39+-12 mL/min; P<.05). Human VEGF mRNA was expressed in
the transfected ischemic muscles as long as 14 days after gene transfer. Based on reporter plasmid expression, transfection efficiency was sixfold higher in ischemic muscles than in nonischemic control muscles. Conclusions: These results suggest the feasibility of employing direct IM transfer of naked VEGF plasmid DNA to optimize treatment of acute limb ischemia.

L14 ANSWER 20 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999391803 EMBASE
TI Gene therapy with vascular endothelial growth factor for inoperable coronary artery disease.
AU Symes J.F.; Losordo D.W.; Vale P.R.; Lathi K.G.; Esakof D.D.; Mayskiy M.; Isner J.M.; Schaff H.V.; Atkinson A.W.; Vincent C.K.; Pham S.M.; Stanbridge R.D.L.; Horowitz S.; Thomas N.J.
CS Dr. J.F. Symes, 11 Nevins St/306, Boston, MA 02135, United States. jsymes@semc.org
SO Annals of Thoracic Surgery, (1999) 68/3 (830-837).
Refs: 21
ISSN: 0003-4975 CODEN: ATHSAK
PUI S 0003-4975(99)00807-3
CY United States
DT Journal; Conference Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
LA English
SL English
AB Background. Patients presenting with medically intractable angina who have undergone previous coronary bypass (CABG) and/or percutaneous revascularization procedures are frequently deemed 'inoperable' based on angiographic findings of diffuse distal disease or a lack of available conduits. We initiated a phase I clinical trial to assess the safety and bioactivity of intramyocardial transfection of plasmid DNA encoding for the angiogenic mitogen vascular endothelial growth factor (***phVEGF165***) in such patients. Methods. ***phVEGF165*** (125 .mu.g, n = 10; 250 .mu.g, n = 10) was injected directly into the myocardium through a mini left anterior thoracotomy as sole therapy in 20 patients (15 male, 5 female, age 48 to 74 years) with class III or IV angina, reversible ischemia on stress sestamibi scans, and 'inoperable' coronary artery disease. Results. All patients tolerated surgery uneventfully and were extubated on the table. No perioperative myocardial infarction, hemodynamic instability, or change in ventricular function occurred. Mean hospital stay was 3.9 days. There was one late death (4 months). Plasma VEGF protein level increased from 30.6 .+-. 4.1 pg/mL pretreatment to 73.7 .+-. 10.1 pg/mL 14 days posttreatment (p = 0.0002) and returned to baseline by day 90. All 16 patients followed to day 90 reported a reduction in angina (nitroglycerin use/week = 60.2 .+-. 4.9 preop vs 3.5 .+-. 1.6 at 90 days; p < 0.0001). Seventy percent (7 of 10) patients were completely angina free at 6 months. A reduction in ischemic defects on single photon emission computerized tomography sestamibi scans was observed in 13 of 17 patients at 60 days (7 of 8 in the 250-.mu.g group). Stress perfusion score decreased from 19.4 .+-. 3.7 at baseline to 15.9 .+-. 3.4 at 60 days (p = 0.025). Angiographic evidence of improved collateral filling of at least one occluded vessel was observed in all patients evaluated at day 60. Conclusions. Direct myocardial gene transfer with ***phVEGF165*** via a mini-thoracotomy can be performed safely and may result in significant symptomatic improvement in patients with 'inoperable' coronary artery disease.

L14 ANSWER 21 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999329010 EMBASE
TI Angiogenesis and gene therapy in man. Dream or reality?.
AU Amant C.; Berthou L.; Walsh K.
CS Dr. K. Walsh, Cardiovascular Research Unit, St Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA 02135, United States. kwalsh@opal.tufts.edu
SO Drugs, (1999) 58/SPEC.ISS. 1 (33-36).
Refs: 15
ISSN: 0012-6667 CODEN: DRUGAY
CY New Zealand
DT Journal; Conference Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Preclinical studies indicate that angiogenic growth factors can stimulate the development of collateral arteries in animal models of peripheral or myocardial ischaemia, a concept termed 'therapeutic angiogenesis'. The goal of this review is to provide a brief overview of the advantages and disadvantages of gene versus recombinant protein therapy for therapeutic angiogenesis. We also discuss different options for delivering genes to patients, including plasmids and modified viral vectors. Recently, the safety and potential utility of gene therapy for ischaemic disease were demonstrated in 3 clinical trials involving the delivery of plasmid DNA encoding the 165 amino acid isoform of human vascular endothelial growth factor (***phVEGF165***), a factor that specifically promotes the proliferation and migration of vascular endothelial cells. Two trials involved the administration of ***phVEGF165*** for peripheral arterial disease. In one trial, the plasmid was administered to the arterial wall from a hydrogel-coated angioplasty balloon, while a second trial examined the direct injection of ***phVEGF165*** into the skeletal muscle of the affected limb. More recently, ***phVEGF165*** was directly injected into ischaemic myocardium. In all these trials, it appears that administration of ***phVEGF165*** led to improvements in tissue perfusion.

L14 ANSWER 22 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999196267 EMBASE
TI Constitutive expression of ***phVEGF165*** after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia [4].
AU Arveschoug A.; Christensen K.S.
CS Dr. A. Arveschoug, Department of Clinical Physiology, Aalborg Hospital, Aalborg, Denmark
SO Circulation, (8 Jun 1999) 99/22 (2967-2968).
Refs: 2
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Letter
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LA English

L14 ANSWER 23 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 97143521 EMBASE
DN 1997143521
TI Passivation of metallic stents after arterial gene transfer of ***phVEGF165*** inhibits thrombus formation and intimal thickening.
AU Van Belle E.; Tio F.O.; Chen D.; Maillard L.; Chen D.; Kearney M.; Isner J.M.
CS Dr. J.M. Isner, St. Elizabeth's Medical Center, Department of Medicine, Tufts University School of Medicine, 736 Cambridge Street, Boston, MA 02135, United States. jisner@opal.tufts.edu
SO Journal of the American College of Cardiology, (1997) 29/6 (1371-1379).
Refs: 46
ISSN: 0735-1097 CODEN: JACCDI
PUI S 0735-1097(97)00049-1
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
LA English
SL English
AB Objectives. This study sought to test the hypothesis that direct gene transfer of an endothelial cell mitogen could passivate metallic stents by accelerating endothelialization of the prosthesis. Background. Thrombosis and restenosis comprise the principal clinical manifestations of compromised biocompatibility of endovascular stents. Previous studies have demonstrated that endothelial recovery at sites of balloon injury is a critical determinant of consequent intimal thickening and mural thrombus. We therefore investigated the potential for an endothelial cell mitogen delivered as plasmid DNA to optimize stent biocompatibility. Methods. Naked plasmid DNA encoding vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF) (***phVEGF165***) was delivered locally using a hydrogel-coated balloon angioplasty catheter to 16 rabbit iliac arteries in which metallic stents had been placed at the site of balloon injury; the contralateral iliac artery of each rabbit was balloon injured and stented but not transfected. Results. Stent endothelialization was accelerated by ***phVEGF165*** gene transfer (87.38 .+-. 5.06% vs. 33.13 .+-. 9.73% [mean .+-. SEM] of the planimetered stent surface in the treated vs. contralateral limb, p = 0.005). This was associated with a significant reduction in mural thrombus (3.7 .+-. 2.4% vs. 32.7 .+-. 9.7%, p = 0.01) at day 7 and intimal thickening (maximal intimal area 0.61 .+-. 0.09 vs. 1.44 .+-. 0.12 mm2, p < 0.0001) at day 28. No benefit was observed from pCMV-luciferase in 14 similarly instrumented control rabbits. Conclusions. These findings indicate that arterial gene transfer of naked plasmid DNA encoding for an endothelial cell mitogen may successfully passivate endovascular stents by accelerating stent endothelialization, thereby reducing in-stent thombus and obstruction due to intimal thickening.

L14 ANSWER 24 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 97004735 EMBASE
DN 1997004735
TI Accelerated restitution of endothelial integrity and endothelium-dependent function after ***phVEGF165*** gene transfer.
AU Asahara T.; Chen D.; Tsurumi Y.; Kearney M.; Rossow S.; Passeri J.; Symes J.F.; Isner J.M.
CS Dr. J.M. Isner, St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA 02135, United States
SO Circulation, (1996) 94/12 (3291-3302).
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
AB Background: Delinquent reendothelialization (rET) has been shown to have a permissive, if not facilitatory, impact on smooth muscle cell

proliferation. This inverse relation has been attributed to certain functions of the endothelium, including barrier regulation of permeability, thrombogenicity, and leukocyte adherence, as well as production of growth inhibitory molecules. Accordingly, the present investigation was designed to test the hypothesis that an endothelial cell (EC) mitogen could serve as the basis for a novel gene therapy strategy designed to facilitate EC regeneration, reduce neointimal thickening, and promote recovery of EC dysfunction after balloon injury. Methods and Results: New Zealand White rabbits underwent simultaneous balloon injury and gene transfer of one femoral artery with ***phVEGF165*** , encoding the 165-amino acid isoform of vascular endothelial growth factor (VEGF), or pGSVLacZ. In each animal transfected with ***phVEGF165*** or pGSVLacZ, the contralateral femoral artery was also subjected to balloon injury but not to gene transfer. For pGSVLacZ, rET remained incomplete at 4 weeks after transfection; in contrast, ***phVEGF165*** produced prompt rET, which was 95% complete by 1 week. Furthermore, rET in the contralateral, balloon-injured, nontransfected limb of the VEGF group was similarly accelerated. Consequently, intimal thickening was diminished, thrombotic occlusion was less frequent, and recovery of EC- dependent vasomotor reactivity was accelerated in VEGF transfectants compared with control animals. A similar benefit was observed for the contralateral, balloon-injured, nontransfected limb. Conclusions: Catheter-mediated, site- specific arterial gene transfer of ***phVEGF165*** can accelerate rET at local and remote sites, leading to inhibition of neointimal thickening, reduction in thrombogenicity, and restoration of endothelium dependent vasomotor reactivity. These findings support the notion that gene transfer encoding for an EC-specific mitogen may be useful for preventing the complications, including restenosis, of balloon angioplasty.

L14 ANSWER 25 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 97004734 EMBASE
DN 1997004734
TI Direct intramuscular gene transfer of naked DNA encoding vascular endothelial growth factor augments collateral development and tissue perfusion.
AU Tsurumi Y.; Takeshita S.; Chen D.; Kearney M.; Rossow S.T.; Passeri J.; Horowitz J.R.; Symes J.F.; Isner J.M.
CS Dr. J.M. Isner, St Elizabeth's Med. Ctr. of Boston, 736 Cambridge St, Boston, MA 02135, United States
SO Circulation, (1996) 94/12 (3281-3290).
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
AB Background: Striated muscle has been shown to be capable of taking up and expressing foreign genes transferred in the form of naked plasmid DNA, although typically with a low level of gene expression. In the case of genes that encode secreted proteins, however, low transfection efficiency may not preclude bioactivity of the secreted gene product. Accordingly, we investigated the hypothesis that intramuscular (IM) gene therapy with naked plasmid DNA encoding vascular endothelial growth factor (VEGF) could augment collateral development and tissue perfusion in an animal model of hindlimb ischemia. Methods and Results: Ten days after ischemia was induced in one rabbit hindlimb, 500 .mu.g of ***phVEGF165*** , or the reported gene LacZ, was injected IM into the ischemic hindlimb muscles. Thirty days later, angiographically recognizable collateral vessels an histologically identifiable capillaries were increased in VEGF transfectants compared with controls. This augmented vascularity improved perfusion to the ischemic limb, documented by a superior calf blood pressure ratio for ***phVEGF165*** (0.85.+-.0.05) versus controls (0.64.+-.0.05, P<.01), improved blood flow in the ischemic limb (measured with an intra-arterial Doppler wire) at rest (***phVEGF165*** =21.3.+-.3.9 mL/min, control=14.6.+-.1.6 mL/min, P<.01) and after a vasodilator (***phVEGF165*** =54.2.+-.12.0 mL/min control=37.3.+-.8.9 mL/min, P<.01) and increased microspheres in the adductor (***phVEGF165*** =4.3.+-.1.6 mL .cntdot. min- 1 .cntdot. 100 g of tissue-1, control=2.9.+-.1.2 mL .cntdot. min-1 .cntdot. 100 g of tissue-1, P<.05) and gastrocnemius (***phVEGF165*** =3.9.+-.1.0 mL .cntdot. min-1 .cntdot. 100 g of tissue-1, control=2.8.+-.1.4 mL .cntdot. min-1 .cntdot. 100 g of tissue-1, P<.05) muscles of the ischemic limb. Conclusions: Ischemic skeletal muscle represents a promising target for gene therapy with naked plasmid DNA. IM transfection of genes encoding angiogenic cytokines, particularly those that are naturally secreted by intact cells, may constitute an alternative treatment strategy for patients with extensive peripheral vascular disease in whom the use of intravascular catheter-based gene transfer is compromised and/or prohibited.

L14 ANSWER 26 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 96331554 EMBASE
DN 1996331554
TI Therapeutic angiogenesis following arterial gene transfer of vascular endothelial growth factor in a rabbit model of hindlimb ischemia.
AU Takeshita S.; Weir L.; Chen D.; Zheng L.P.; Riessen R.; Bauters C.; Symes J.F.; Ferrara N.; Isner J.M.
CS Department of Medicine, St Elizabeth's Medical Center Boston, Tufts University School of Medicine,Boston, MA 02135, United States
SO Biochemical and Biophysical Research Communications, (1996) 227/2 (628-635).
ISSN: 0006-291X CODEN: BBRCA
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
AB The plasmid ***phVEGF165*** , expressing the 165-amino-acid isoform of vascular endothelial growth factor (VEGF), an endothelial cell specific mitogen, was applied to the polymer coating of an angioplasty balloon and delivered percutaneously to the iliac artery of rabbits in which the femoral artery had been excised to cause hindlimb ischemia. Site-specific transfection of ***phVEGF165*** resulted in augmented development of collateral vessels documented by serial angiograms, and increased capillary density as well as increased capillary/myocyte ratio documented histochemically at necropsy. Consequent amelioration of the hemodynamic deficit in the ischemic limb was documented by improvement in the calf blood pressure ratio (ischemic/normal limb) to 0.70 .+-. 0.08 in the VEGF-transfected group vs 0.50 .+-. 0.18 in controls (p < 0.05). These findings suggest that site-specific arterial gene transfer of VEGF165 may achieve physiologically meaningful therapeutic modulation of vascular insufficiency.

L14 ANSWER 27 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 96319084 EMBASE
DN 1996319084
TI Gene transfer of naked DNA encoding for three isoforms of vascular endothelial growth factor stimulates collateral development in vivo.
AU Takeshita S.; Tsurumi Y.; Couffinahl T.; Asahara T.; Bauters C.; Symes J.; Ferrara N.; Isner J.M.
CS St. Elizabeth's Medical Center, 736 Cambridge Street,Boston, MA 02135, United States
SO Laboratory Investigation, (1996) 75/4 (487-501).
ISSN: 0023-6837 CODEN: LAINAW
CY United States
DT Journal; Article
FS 022 Human Genetics
LA English
SL English
AB Vascular endothelial growth factor (VEGF) is a naturally secreted endothelial cell-specific mitogen. We investigated the hypothesis that naked DNA encoding for VEGF could be used in a strategy of arterial gene therapy to stimulate collateral artery development. Plasmid DNA encoding each of the three principal human VEGF isoforms (phVEGF121, ***phVEGF165*** , or phVEGF189) was applied to the hydrogel polymer coating of an angioplasty balloon and delivered percutaneously to one iliac artery of rabbits with operatively induced hindlimb ischemia. Compared with control animals transfected with LacZ, site-specific transfection of phVEGF resulted in augmented collateral vessel development documented by serial angiography, and improvement in calf blood pressure ratio (ischemic to normal limb), resting and maximum blood flow, and capillary to myocyte ratio. Similar results were obtained with phVEGF121, ***phVEGF165*** , and phVEGF189, which suggests that these isoforms are biologically equivalent with respect to in vivo angiogenesis. The fact that viral or other adjunctive vectors were not required further suggests that secreted gene products may have potential therapeutic utility even when the number of successfully transfected cells remains low. Arterial gene transfer of naked DNA encoding for a secreted angiogenic cytokine, thus, represents a potential alternative to recombinant protein administration for stimulating collateral vessel development.

L14 ANSWER 28 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 96242268 EMBASE
DN 1996242268
TI Clinical evidence of angiogenesis after arterial gene transfer of ***phVEGF165*** in patient with ischaemic limb.
AU Isner J.M.; Pieczek A.; Schainfeld R.; Blair R.; Haley L.; Asahara T.; Rosenfield K.; Razvi S.; Walsh K.; Symes J.F.
CS St. Elizabeth's Medical Center,Boston, MA 02135, United States
SO Lancet, (1996) 348/9024 (370-374).
ISSN: 0140-6736 CODEN: LANCAO
CY United Kingdom
DT Journal; Article
FS 006 Internal Medicine
009 Surgery
LA English
SL English
AB Background: Preclinical findings suggest that intra-arterial gene transfer of a plasmid which encodes for vascular endothelial growth factor (VEGF) can improve blood supply to the ischaemic limb. We have used the method in a patient. Methods: Our patient was the eighth in a dose-ranging series. She was aged 71 with an ischaemic right leg. We administered 2000 .mu.g human plasmid ***phVEGF165*** that was applied to the hydrogel polymer coating of an angioplasty balloon. By inflating the balloon, plasmid DNA was transferred to the distal popliteal artery. Findings: Digital subtraction angiography 4 weeks after gene therapy showed an increase in collateral vessels at the knee, mid-tibial, and ankle levels, which persisted at a 12-week view. Intra-arterial doppler-flow studies showed increased resting and maximum flows (by 82% and 72%, respectively). Three spider angiomas developed on the right foot/ankle about a week after gene transfer; one lesion was excised and revealed proliferative endothelium, the other two regressed. The patient developed oedema in her right leg,

which was treated successfully. Interpretation: Administration of endothelial cell mitogens promotes angiogenesis in patients with limb ischaemia.

L14 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:74103 CAPLUS
DN 135:102832
TI Intramyocardial injection of DNA encoding vascular endothelial growth factor in a myocardial infarction model
AU Kloner, Robert A.; Dow, Joan; Chung, Gene; Kedes, Larry H.
CS Heart Institute, Good Samaritan Hospital, University of Southern California, Los Angeles, CA, USA
SO Journal of Thrombosis and Thrombolysis (***2000***), 10(3), 285-289
CODEN: JTTHFF; ISSN: 0929-5305
PB Kluwer Academic Publishers
DT Journal
LA English
AB In a previous study, we obsd. that one injection of 500 .mu.g of DNA for the plasmid encoding for vascular endothelial growth factor (ph VEGF165) into one site in a rat myocardial infarction model resulted in neovascularization confined to angiomatous structures that did not contribute to regional myocardial blood flow. The purpose of the present study was to det. whether a lower dose (125 .mu.g DNA), which is the same as that being used in some clin. trials, injected into four sep. sites could enhance collateral flow and vascularity to the ischemic bed without inducing angiomas. Rats received injections of 125 .mu.g DNA of the plasmid encoding ***phVEGF165*** or control DNA at four sep. sites within the anterior free wall of the left ventricle (LV) supplied by the left coronary artery. The left coronary artery was ligated and hearts analyzed at 4 wk. In vitro studies confirmed that the ***phVEGF165*** used was capable of producing VEGF polypeptide in mammalian cells. The infarct size (percentage of endocardial circumference that infarcted) was similar in controls (42%) and treated hearts (39%); the LV cavity area did not differ between groups. The no. of vascular structures per high-power field within the infarct scar was 10.50 in controls and 10.00 in ***phVEGF165*** -treated rats. Relative regional myocardial blood flow detd. by radioactive microspheres and expressed as a ratio of radioactive counts within the scar divided by radioactive counts in the noninfarcted ventricular septum was similar in control (0.74) and treated hearts (0.88). No angiomatous structures were obsd. Injections of 125 .mu.g of DNA of ***phVEGF165*** into myocardium to become ischemic had no effect on infarct size or LV cavity size. Unlike higher doses of 500 .mu.g of DNA, it did not cause gross angiomatous structures; however, it failed to improve neovascularization or regional myocardial blood flow in this rodent model of acute myocardial infarction.
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1997:366376 CAPLUS
DN 126:325520
TI Method for treating ischemic tissue using a nucleic acid expressing an angiogenic protein
IN Isner, Jeffrey M.
PA St. Elizabeth's Medical Center of Boston, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9714307	A1	19970424	WO 1996-US16723	19961018 <--
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6121246	A	20000919	US 1995-545998	19951020 <--
AU 9674548	A1	19970507	AU 1996-74548	19961018 <--
AU 725290	B2	20001012		
EP 883343	A1	19981216	EP 1996-936690	19961018 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11514366	T2	19991207	JP 1996-516039	19961018 <--
PRAI US 1995-545998	A	19951020		
WO 1996-US16723	W	19961018		

AB A method for treating ischemic tissue (e.g. muscle) in a mammal comprises injecting the tissue with an effective amt. of a nucleic acid capable of expressing an angiogenic protein. The method may be used to treat any ischemic tissue, i.e., a tissue having a deficiency in blood as the results of an ischemic disease. Ischemic diseases include e.g. limb ischemia.

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FULL ESTIMATED COST		0.06	157.15

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L19 5 DUP REM L18 (3 DUPLICATES REMOVED)

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L19 ANSWER 1 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:279710 BIOSIS
DN PREV200200279710
TI Vascular endothelial growth factor C (***VEGF*** - ***C***) protein and gene, mutants thereof, and uses thereof.
AU Alitalo, Kari (1); Joukov, Vladimir
CS (1) Helsinki Finland
ASSIGNEE: Licentia Ltd, Helsinki, Finland; Ludwig Institute for Cancer Research
PI US 6361946 March 26, 2002
SO Official Gazette of the United States Patent and Trademark Office Patents, (Mar. 26, 2002) Vol. 1256, No. 4, pp. No Pagination.
http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DT Patent
LA English
AB Provided are purified and isolated ***VEGF*** - ***C*** polypeptides capable of binding to at least one of KDR receptor tyrosine kinase (VEGFR-2) and Flt4 receptor tyrosine kinase (VEGFR-3); analogs of such peptides that have ***VEGF*** - ***C*** -like or VEGF-like ***biological*** ***activities*** or that are VEGF or ***VEGF*** - ***C*** inhibitors; polynucleotides encoding the polypeptides; vectors and host cells that embody the polynucleotides; pharmaceutical compositions and diagnostic reagents comprising the polypeptides; and methods of making and using the polypeptides.

L19 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2002:316248 BIOSIS
DN PREV200200316248
TI Relative effects of VEGF-A and ***VEGF*** - ***C*** on endothelial cell proliferation, migration, and PAF synthesis: Role of neuropilin-1.
AU Bernatchez, Pascal N.; Rollin, Simon; Soker, Shay; Sirois, Martin G. (1)
CS (1) Montreal Heart Institute (Research Center), 5000 Belanger Street, Montreal, Qc, H1T 1C8: mgsirois@icm.umontreal.ca Canada
SO Journal of Cellular Biochemistry, (2002) Vol. 85, No. 3, pp. 629-639.
http://www.interscience.wiley.com/jpages/0730-2312/. print.
ISSN: 0730-2312.
DT Article
LA English
AB Vascular endothelial growth factor (VEGF-A) is an inducer of endothelial cell (EC) proliferation, migration, and synthesis of inflammatory agents such as platelet-activating factor (PAF). Recently, neuropilin-1 (NRP-1) has been described as a coreceptor of KDR which potentiates VEGF-A activity. However, the role of NRP-1 in numerous VEGF-A activities remains unclear. To assess the contribution of NRP-1 to VEGF-A mediated EC proliferation, migration, and PAF synthesis, we used porcine aortic EC (PAEC) recombinantly expressing Flt-1, NRP-1, KDR or KDR and NRP-1. Cells were stimulated with VEGF-A, which binds to Flt-1, KDR and NRP-1, and

VEGF - ***C*** , which binds to KDR only. VEGF-A was 12.4-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation in PAEC-KDR. VEGF-A and ***VEGF*** - ***C*** showed similar potency to mediate PAEC-KDR proliferation, migration, and PAF synthesis. On PAEC-KDR/NRP-1, VEGF-A was 28.6-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation and PAEC-KDR/NRP-1 proliferation (1.3-fold), migration (1.7-fold), and PAF synthesis (4.6-fold). These results suggest that cooperative binding of VEGF-A to KDR and NRP-1 enhances KDR phosphorylation and its ***biological*** ***activities*** . Similar results were obtained with bovine aortic EC that endogenously express both KDR and NRP-1 receptors. In contrast, stimulation of PAEC-Flt-1 and PAEC-NRP-1 with VEGF-A or ***VEGF*** - ***C*** did not induce proliferation, migration, or PAF synthesis. In conclusion, the presence of NRP-1 on EC preferentially increases KDR activation by VEGF-A as well as KDR-mediated ***biological*** ***activities*** , and may elicit novel intracellular events. On the other hand, VEGF-A and ***VEGF*** - ***C*** have equipotent ***biological*** ***activities*** on EC in absence of NRP-1.

L19 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:264176 BIOSIS
DN PREV200100264176
TI Comparative biological effects of VEGF and ***VEGF*** - ***C*** on endothelial cells: Role of neuropilin-1 and Flk-1/KDR receptors.
AU Bernatchez, Pascal N. (1); Soker, Shay; Rollin, Simon (1); Sirois, Martin G. (1)
CS (1) Montreal Heart Institute, 5000 Belanger St, Montreal, Qc, H1T 1C8 Canada
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1078. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB We have recently shown that Vascular Endothelial Growth Factor (VEGF) activation of Flk-1/KDR promotes migration, proliferation and platelet-activating factor (PAF) synthesis. Neuropilin-1 (NRP1) has been described as a coreceptor of Flk-1/KDR which potentiates VEGF165 activity. However, the role of NRP1 in numerous VEGF activities remains unclear. To assess the contribution of NRP1 in VEGF-mediated EC proliferation, migration and PAF synthesis, we used porcine aortic EC (PAEC) which do not express VEGF receptors, and transfected them with KDR and/or NRP1 cDNA. A preliminary study showed that unlike VEGF, ***VEGF*** - ***C*** does not bind to NRP-1. In the present study, we compare the biological effects of VEGF and ***VEGF*** - ***C*** in EC. First, we observed that VEGF was 2.7-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation in PAEC-KDR. However, VEGF and ***VEGF*** - ***C*** showed similar potency to mediate PAEC-KDR proliferation, migration and PAF synthesis. This suggests that maximal phosphorylation of KDR is above the optimal activation required for its maximal ***biological*** ***activities*** . On PAEC-KDR-NRP1, VEGF was 6.6-fold more potent than ***VEGF*** - ***C*** in inducing KDR phosphorylation. In addition, VEGF was more potent than ***VEGF*** - ***C*** in eliciting PAEC-KDR-NRP1 proliferation (1.33-fold), migration (1.73-fold) and PAF synthesis (3.60-fold). This suggests that cooperative binding of VEGF to KDR and NRP1 enhances KDR phosphorylation and subsequently proliferation, migration and PAF synthesis. Stimulation of PAEC-NRP1 with VEGF or ***VEGF*** - ***C*** did not induce the activities described above. In conclusion, VEGF and ***VEGF*** - ***C*** have equipotent ***biological*** ***activities*** in the absence of NRP1. Cooperative binding of VEGF to NRP1 and KDR potentiated VEGF-mediated activity compared with ***VEGF*** - ***C*** . These results suggest that the presence of NRP1 on EC might increase or sustain the response upon KDR activation.

L19 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2001:385230 BIOSIS
DN PREV200100385230
TI Alternative splicing of the human VEGFGR-3/FLT4 gene as a consequence of an integrated human endogenous retrovirus.
AU Hughes, David C. (1)
CS (1) Reproductive Biology and Genetics Group, Division of Medicine, University of Birmingham, Birmingham, B15 2TT: d.c.hughes@bham.ac.uk UK
SO Journal of Molecular Evolution, (August, 2001) Vol. 53, No. 2, pp. 77-79. print.
ISSN: 0022-2844.
DT Article
LA English
SL English
AB The vascular endothelial growth factor receptor 3 (VEGFR-3/FLT4) is a receptor tyrosine kinase that regulates angiogenesis and vasculogenesis in response to the binding of the ligands ***VEGF*** - ***C*** and VEGF-D. Mutations in VEGFR-3 have been identified in patients with primary lymphoedema. It has been noted previously that whilst in the mouse there is only a single Vegfr-3 transcript, in humans there are two transcripts of 5.8 and 4.5 kb, of which the shorter encodes a protein that lacks the C-terminal 65 amino acids. These two isoforms also differ in their ***biological*** ***activity*** . Analysis of the human VEGFR-3 cDNA and genomic sequence reveals that these two isoforms arise by alternative splicing of the terminal exons. The shorter transcript is generated by splicing into the long terminal repeat of a human endogenous retrovirus located between the last two exons, thus explaining the lack of the shorter transcript in the mouse. The retention of the retroviral sequences in the FLT4 locus suggests that this retrotransposition event has contributed significant additional function to this gene. This provides support for a role for integrated retroviruses in modulating gene activity and participating in evolutionary processes.

L19 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
AN 2000:69739 BIOSIS
DN PREV200000069739
TI Lymphangiogenesis and ***biological*** ***activity*** of vascular endothelial growth factor (***VEGF***)- ***C*** .
AU Mandriota, Stefano J. (1); Pepper, Michael S. (1)
CS (1) Departement de Morphologie, Centre Medical Universitaire, 1, rue Michel Servet, 1211, Geneve, 4 Switzerland
SO Journal de la Societe de Biologie, (1999) Vol. 193, No. 2, pp. 159-163. ISSN: 1295-0661.
DT Article
LA French
SL English; French
AB Vascular endothelial growth factor (***VEGF***)- ***C*** is a new member of the VEGF family, a group of polypeptide growth factors which play key roles in the physiology and pathology of many aspects of the cardiovascular system, including vasculogenesis, hematopoiesis, angiogenesis and vascular permeability. VEGF signaling in endothelial cells occurs through three tyrosine kinase receptors (VEGFRs), expressed by endothelial cells and hematopoietic precursors. With respect to the first VEGF described, VEGF-A, which is an endothelial cell specific mitogen and key angiogenic factor, ***VEGF*** - ***C*** seems to play a major role in the development of the lymphatic system. This may reflect the different binding properties of VEGFs to VEGFRs, in that VEGF-A binds to VEGFR-1 and -2, whereas ***VEGF*** - ***C*** acts through VEGFR-3, whose expression becomes restricted to lymphatics and certain veins during development. However, the finding that ***VEGF*** - ***C*** also binds to and activates VEGFR-2 may explain why it induces angiogenesis under certain conditions, which makes it relevant to experimental or clinical settings in which one would wish to block or to stimulate angiogenesis. In this paper we briefly discuss current knowledge on the ***biological*** ***activity*** of ***VEGF*** - ***C*** , emphasizing that, as has already been shown for a number of other angiogenic factors, the biological effects of ***VEGF*** - ***C*** are strictly dependent on the activity of other angiogenic regulators present in the microenvironment of the responding endothelial cells.

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=> dhis
DHIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

    (FILE 'HOME' ENTERED AT 18:34:27 ON 16 JUL 2003)

    FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 18:36:48 ON 16 JUL 2003
L1        1907 S VEGF A OR VEGF C
L2         163 S VEGF A AND VEGF C
L3          81 DUP REM L2 (82 DUPLICATES REMOVED)
L4           1 S L3 AND MTS
L5           0 S L3 AND (HUVAC AND COS)
L6           0 S L3 AND HUVAC
L7          16 S L1 AND BIOLOGICAL ACTIV?
L8          10 DUP REM L7 (6 DUPLICATES REMOVED)
L9          71 S PHVEGF165
L10          3 S PHVEGF2
L11         74 S L9 OR L10
L12          0 S L11 AND BIOLOGICAL ACTIV?
L13         44 DUP REM L11 (30 DUPLICATES REMOVED)
L14         30 S L13 AND PY<=2000
L15          0 S L14 AND HUVAC
L16          0 S L14 AND HUVEC

    FILE 'STNGUIDE' ENTERED AT 18:59:29 ON 16 JUL 2003

    FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 19:00:21 ON 16 JUL 2003
L17        779 S VEGF C
L18          8 S L17 AND BIOLOG? ACTIVI?
L19          5 DUP REM L18 (3 DUPLICATES REMOVED)

=> s l17 and HUVEC
L20          9 L17 AND HUVEC

=> dup rem l20
PROCESSING COMPLETED FOR L20
L21          9 DUP REM L20 (0 DUPLICATES REMOVED)

=> s l21 not l19
L22          9 L21 NOT L19
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=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y

L22 ANSWER 1 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:196564 BIOSIS
DN PREV200300196564
TI Malignant mesothelioma growth inhibition by agents that target the VEGF and ***VEGF*** - ***C*** autocrine loops.
AU Masood, Rizwan (1); Kundra, Ajay; Zhu, Sutao; Xia, Guangbin; Scalia, Pierluigi; Smith, D. Lynne; Gill, Parkash S.
CS (1) USC/Norris Cancer Center, 1441 East-lake Ave, Rm. NOR 6330, MC 9176, Los Angeles, CA, 90033-9176, USA: masood@usc.edu USA
SO International Journal of Cancer, (1 May 2003) Vol. 104, No. 5, pp. 603-610. print.
ISSN: 0020-7136.
DT Article
LA English
AB Malignant mesothelioma (MM) is a locally aggressive tumor that originates from the mesothelial cells of the pleural and sometimes peritoneal surface. Conventional treatments for MM, consisting of chemotherapy or surgery give little survival benefit to patients, who generally die within 1 year of diagnosis. Hence, there is an urgent need for the development of alternative therapies. Vascular endothelial growth factor (VEGF) is an autocrine growth factor for MM. The closely related molecule, ***VEGF*** - ***C*** , is also implicated in malignant mesothelioma growth. ***VEGF*** - ***C*** and its cognate receptor VEGFR-3 are co-expressed in mesothelioma cell lines. A functional ***VEGF*** - ***C*** autocrine growth loop was demonstrated in mesothelioma cells by targeting ***VEGF*** - ***C*** expression and binding to VEGFR-3. The ability of novel agents that reduce the levels of VEGF and ***VEGF*** - ***C*** to inhibit mesothelioma cell growth in vitro was assessed. Antisense oligonucleotide (ODN) complementary to VEGF that inhibited VEGF and ***VEGF*** - ***C*** expression simultaneously specifically inhibited mesothelioma cell growth. Similarly, antibodies to VEGF receptor (VEGFR-2) and ***VEGF*** - ***C*** receptor (VEGFR-3) were synergistic in inhibiting mesothelioma cell growth. In addition, a diphtheria toxin-VEGF fusion protein (DT-VEGF), which is toxic to cells that express VEGF receptors was very effective in inhibiting mesothelioma cell growth in vitro. These results indicate that targeting VEGF and ***VEGF*** - ***C*** simultaneously may be an effective therapeutic approach for malignant mesothelioma.

L22 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:97225 BIOSIS
DN PREV200300097225
TI ***VEGF*** - ***C*** mediates cyclic pressure-induced endothelial cell proliferation.
AU Shin, Hainsworth Y.; Smith, Michael L.; Toy, Karen J.; Williams, P. Mickey; Bizios, Rena (1); Gerritsen, Mary E.
CS (1) Dept. of Biomedical Engineering, Rensselaer Polytechnic Institute, 110 8th St., Jonsson Engineering Center, Rm. 7049, Troy, NY, 12180-3590, USA: bizios@rpi.edu USA
SO Physiological Genomics, (January 2003, 2003) Vol. 11, pp. 245-251. print.
ISSN: 1094-8341.
DT Article
LA English
AB Mechanical forces modulate endothelial cell functions through several mechanisms including regulation of gene transcription. In the present study, gene transcription by human umbilical vein endothelial cells (***HUVEC***) either maintained under control pressure (that is, standard cell culture conditions equivalent to 0.15 mmHg sustained hydrostatic pressure) or exposed to 60/20 mmHg sinusoidal pressures at 1 Hz were compared using Affymetrix GeneChip microarrays to identify cellular/molecular mechanisms associated with endothelial cell responses to cyclic pressure. Cyclic pressure selectively affected transcription of 14 genes that included a set of mechanosensitive proteins involved in hemostasis (tissue plasminogen activator), cell adhesion (integrin-alpha2), and cell signaling (Rho B, cytosolic phospholipase A2), as well as a unique subset of cyclic pressure-sensitive genes such as vascular endothelial growth factor (***VEGF***)- ***C*** and transforming growth factor (TGF)-beta2. The present study also provided first evidence that ***VEGF*** - ***C*** , the most highly induced gene under 60/20 mmHg, mediated ***HUVEC*** proliferation in response to this cyclic pressure. Cyclic pressure is, therefore, a mechanical force that modulates endothelial cell functions (such as proliferation) by activating a specific transcriptional program.

L22 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:430955 BIOSIS
DN PREV200200430955
TI DNA chip analysis of Akt-regulated genes in endothelial cells reveals activation of many proangiogenic pathways.
AU Kim, Hyo-Soo (1); Ivashchenko, Yuri; Walsh, Kenneth
CS (1) Boston University Medical Center, Boston, MA USA
SO Journal of the American College of Cardiology, (March 6, 2002) Vol. 39, No. 5 Supplement A, pp. 232A-233A. http://www.cardiosource.com/config/jacc/default.htm. print.
Meeting Info.: 51st Annual Scientific Session of the American College of Cardiology Atlanta, GA, USA March 17-20, 2002
ISSN: 0735-1097.
DT Conference
LA English

L22 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:313307 BIOSIS
DN PREV200200313307
TI Temporal endothelial gene expression in response to C5a.
AU Albrecht, Eric (1); Varambally, Sooryanarayana (1); Kumar-Sinha, Chandan (1); Barrette, Terrence (1); Sarma, J. Vidya (1); Chinnaiyan, Arul (1); Ward, Peter A. (1)
CS (1) University of Michigan, 1150 W. Medical Center Dr., 7526 MSRB I, Ann Arbor, MI, 48109 USA
SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A200. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DT Conference
LA English
AB The endothelium plays a critical role in the inflammatory process, which involves expression and release of proteins aiding in diapedesis of neutrophils and activation of the clotting system. Part of the inflammatory response involves the complement cascade and the production of the anaphylatoxin C5a. C5a is known to induce both anti-inflammatory and pro-inflammatory responses in the endothelium, yet the molecular mechanism(s) that control these processes remains unclear. We investigated, by microarray analysis, the temporal gene expression of human umbilical vein endothelial cell's (***HUVEC*** 's) stimulated with human C5a (50 ng/ml) for 30 min, 2 hrs, or 4 hrs. This was compared with the genetic expression of ***HUVEC*** 's stimulated with human TNFalpha (1 ng/ml) or LPS (1mug/ml) for 4 hrs. ***HUVEC*** 's stimulated with C5a induced progressive increases in gene expression ratios for cell adhesion and cytokine/chemokine genes (e.g., E-Selectin, ICAM-1, TNFAIP3). This coincided with transient increases in gene expressions associated with broad functional activities (e.g., TGFbeta2-early, BTF3-mid, ***VEGF*** - ***C*** -late). Thus, endothelial cells respond to C5a by inducing specific, transient changes coupled with progressive increases in cell adherence and cytokine/chemokine gene activation.

L22 ANSWER 5 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:221122 BIOSIS
DN PREV200200221122
TI Vascular endothelial growth factor (***VEGF***)- ***C*** signaling through FLT-4 (VEGFR-3) mediates leukemic cell proliferation, survival, and resistance to chemotherapy.
AU Dias, Sergio; Choy, Margaret; Alitalo, Kari; Rafii, Shahin (1)
CS (1) Division of Hematology/Oncology, Weill Medical College of Cornell University, 1300 York Ave, Rm C-606, New York, NY, 10021: srafii@mail.med.cornell.edu USA
SO Blood, (March 15, 2002) Vol. 99, No. 6, pp. 2179-2184. http://www.bloodjournal.org/. print.
ISSN: 0006-4971.
DT Article
LA English
AB Similar to solid tumors, growth of leukemias may also be angiogenesis dependent. Furthermore, tyrosine kinase receptors specific to endothelial cells are expressed on certain subsets of leukemias. We have previously demonstrated the existence of a VEGF/VEGFR-2 autocrine loop on leukemic cells that supports their growth and migration. Here, we demonstrate that in response to leukemia-derived proangiogenic and proinflammatory cytokines such as basic fibroblast growth factor and IL-1, endothelial cells release increasing amounts of another vascular endothelial growth factor (VEGF) family member, ***VEGF*** - ***C*** . In turn, interaction of ***VEGF*** - ***C*** with its receptor VEGFR-3 (FLT-4) promotes leukemia survival and proliferation. We demonstrate in 2 cell lines and 5 FLT-4+ leukemias that ***VEGF*** - ***C*** and a mutant form of the molecule that lacks the KDR-binding motif induce receptor phosphorylation, leukemia proliferation, and increased survival, as determined by increased Bcl-2/Bax ratios. Moreover, ***VEGF*** - ***C*** protected leukemic cells from the apoptotic effects of 3 chemotherapeutic agents. Because most leukemic cells release proangiogenic as well as proinflammatory cytokines, our data suggest that the generation of a novel paracrine angiogenic loop involving ***VEGF*** - ***C*** and FLT-4 may promote the survival of a subset of leukemias and protect them from chemotherapy-induced apoptosis. These results identify the ***VEGF*** - ***C*** /FLT-4 pathway as a novel therapeutic target for the treatment of subsets of acute leukemia.

L22 ANSWER 6 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:73116 BIOSIS
DN PREV200200073116
TI Vascular endothelial growth factor (VEGF) receptor-2 antagonists inhibit VEGF- and basic fibroblast growth factor-induced angiogenesis in vivo and in vitro.
AU Tille, J.-C.; Wood, J.; Mandriota, S. J.; Schnell, C.; Ferrari, S.; Mestan, J.; Zhu, Z.; Witte, L.; Pepper, M. S. (1)
CS (1) Department of Morphology, University Medical Center, 1 Rue Michel

Servet, 1211, Geneva, 4: michael.pepper@medecine.unige.ch Switzerland
SO Journal of Pharmacology and Experimental.Therapeutics, (December, 2001) Vol. 299, No. 3, pp. 1073-1085. print.
ISSN: 0022-3565.
DT Article
LA English
AB Exponential tumor growth is angiogenesis-dependent. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are potent angiogenic inducers that act synergistically in vivo and in vitro. We assessed the effect of specific inhibitors of VEGF receptor (VEGFR)-2 tyrosine kinase activity in in vivo and in vitro models of VEGF- and bFGF-induced angiogenesis. In an implant mouse model of angiogenesis, VEGFR-2 inhibitors completely blocked angiogenesis induced by VEGF, and, surprisingly, also inhibited the effect of bFGF to various extents. In vitro, VEGF- and bFGF-induced bovine microvascular and aortic endothelial (BME and BAE) cell collagen gel invasion could be blocked by the VEGFR-2 inhibitors by 100 and appnx90%, respectively. Similar results were obtained with VEGFR-1-IgG and VEGFR-3-IgG fusion proteins and with VEGFR-2
blocking antibodies. Both BME and BAE cells produce VEGF and ***VEGF*** - ***C*** , which is not modulated by bFGF. Thus, the unexpected inhibition of bFGF-induced angiogenesis by VEGFR-2 antagonists reveals a requirement for endogenous VEGF and ***VEGF*** - ***C*** in this process. These findings broaden the spectrum of mediators of angiogenesis that can be inhibited by VEGFR-2 antagonists and highlight the importance of these compounds as agents for inhibiting tumor growth sustained by both VEGF and bFGF.

L22 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:312511 BIOSIS
DN PREV200100312511
TI ***VEGF*** - ***C*** signaling through Flt-4 (VEGFR3) mediates leukemic cell proliferation and survival.
AU Choy, M. (1); Dias, S. (1); Alitalo, R.; Alitalo, K.; Rafii, S. (1)
CS (1) Cornell U. Med. College, New York, NY USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 502a-503a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB Recent findings have documented the relationship between leukemia and angiogenesis. In leukemia, increased bone marrow vessel density and vascular endothelial growth factor (VEGF) plasma levels correlate with poor prognosis. Leukemic cells secrete endothelial growth factors such as VEGF to enhance endothelial cell(EC) survival and proliferation while in turn ECs release growth factors such as GM-CSF to support leukemic cell growth. Given that other VEGF family members may play a role in leukemia biology, we speculated that ***VEGF*** - ***C*** may also modulate leukemic cell growth. ***VEGF*** - ***C*** , which binds VEGFR-2 (KDR) and VEGFR-3(Flt-4), was recently shown to be elaborated by subsets of leukemic cells. Similar to VEGF, ***VEGF*** - ***C*** increases EC migration and proliferation. However, in contrast to VEGF, it is expressed by various ECs including lymphatic EC and primary human umbilical vein EC (***HUVEC***) as well as certain solid and liquid tumors. Since the ***VEGF*** - ***C*** specific receptor, Flt-4, is expressed on primary leukemia cells and cell lines, we hypothesized that it may play a role in leukemia cell growth and survival. In this study, the leukemia cell lines THP-1 and HEL were found to express functional Flt-4 receptors that phosphorylate upon stimulation by either ***VEGF*** - ***C*** or mutant ***VEGF*** - ***C*** (which only signals through Flt-4, but not KDR). Treatment with ***VEGF*** - ***C*** or its mutant in serum free conditions increased THP-1 and HEL proliferation by 20-30% over a 24-48 hr period. Additionally, both ***VEGF*** - ***C*** and its mutant enhanced THP-1 and HEL survival by 30-40%, as determined by Trypan blue exclusion and Annexin V staining. Its pro-survival effects were further demonstrated by an upregulation of the anti-apoptotic protein Bcl-2 in HEL and THP-1 cells following 24 hour serum-free treatment with either ***VEGF*** - ***C*** or its mutant. These results suggest that ***VEGF*** - ***C*** exerts both mitogenic and pro-survival effects on leukemic cells through its receptor Flt-4. Given that ECs as well as leukemic cells secrete ***VEGF*** - ***C*** , its production may support leukemic cell proliferation and survival through a Flt-4 mediated autocrine and/or paracrine mechanism. In this context, we demonstrate that leukemic cells produce pro-inflammatory cytokines such as IL-1 and TNF which increases ***VEGF*** - ***C*** production by ***HUVEC*** , generating a paracrine loop to support leukemia growth and survival. In turn, enhanced leukemia cell survival and proliferation may increase blood vessel density by elevating levels of leukemia-derived proangiogenic factors such as VEGF and FGF-2. These results identify the ***VEGF*** - ***C*** /Flt-4 pathway as a potential target for therapeutic intervention in subsets of human acute leukemias.

L22 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2003:72108 CAPLUS
DN 138:332157
TI ***VEGF*** - ***C*** mediates cyclic pressure-induced endothelial cell proliferation
AU Shin, Hainsworth Y.; Smith, Michael L.; Toy, Karen J.; Williams, P. Mickey; Bizios, Rena; Gerritsen, Mary E.
CS Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, NY, 12180, USA
SO Physiological Genomics (2002), 11(3), 245-251
CODEN: PHGEFP; ISSN: 1094-8341
URL: http://physiolgenomics.physiology.org/cgi/reprint/11/3/245.pdf
PB American Physiological Society
DT Journal; (online computer file)
LA English
AB Mech. forces modulate endothelial cell functions through several mechanisms including regulation of gene transcription. In the present study, gene transcription by human umbilical vein endothelial cells (***HUVEC***) either maintained under control pressure (i.e., std. cell culture conditions equiv. to 0.15 mmHg sustained hydrostatic pressure) or exposed to 60/20 mmHg sinusoidal pressures at 1 Hz were compared using Affymetrix GeneChip microarrays to identify cellular/mol. mechanisms assocd. with endothelial cell responses to cyclic pressure. Cyclic pressure selectively affected transcription of 14 genes that included a set of mechanosensitive proteins involved in hemostasis (tissue plasminogen activator), cell adhesion (integrin-.alpha.2), and cell signaling (Rho B, cytosolic phospholipase A2), as well as a unique subset of cyclic pressure-sensitive genes such as vascular endothelial growth factor (***VEGF***)- ***C*** and transforming growth factor (TGF)-.beta.2. The present study also provided first evidence that ***VEGF*** - ***C*** , the most highly induced gene under 0/20 mmHg, mediated ***HUVEC*** proliferation in response to this cyclic pressure. Cyclic pressure is, therefore, a mech. force that modulates endothelial cell functions (such as proliferation) by activating a specific transcriptional program.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2002:276183 CAPLUS
DN 136:289910
TI Plasmid vector carrying endothelial cell mitogen for gene therapy and assay for cell survival of transiently transfected cells
IN Kearney, Marianne; Isner, Jeffrey M.
PA St. Elizabeth's Medical Center, USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002029082	A1	20020411	WO 2001-US29638	20010921
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001094633	A5	20020415	AU 2001-94633	20010921
US 2002155421	A1	20021024	US 2001-961128	20010921
PRAI US 2000-236767P	P	20000929		
WO 2001-US29638	W	20010921		

AB The present invention provides novel methods for detg. the bioactivity of a plasmid encoding for an endothelial cell mitogen. The invention also provides a method to optimize a plasmid construct for use in a gene therapy procedure. Further, the invention provides a quant. quality control assay for evaluating a batch of plasmid DNA prior to use in a gene therapy treatment. The said endothelial cell mitogens include acidic and basic fibroblast growth factor, VEGF, EGF, transforming growth factor .alpha. and .beta., platelet-derived growth factor, platelet-derived endothelial growth factor, tumor necrosis factor, hepatocyte growth factor and insulin-like growth factor.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 18:34:27 ON 16 JUL 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 18:36:48 ON 16 JUL 2003
L1 1907 S VEGF A OR VEGF C
L2 163 S VEGF A AND VEGF C
L3 81 DUP REM L2 (82 DUPLICATES REMOVED)
L4 1 S L3 AND MTS
L5 0 S L3 AND (HUVAC AND COS)
L6 0 S L3 AND HUVAC
L7 16 S L1 AND BIOLOGICAL ACTIV?
L8 10 DUP REM L7 (6 DUPLICATES REMOVED)
L9 71 S PHVEGF165
L10 3 S PHVEGF2
L11 74 S L9 OR L10
L12 0 S L11 AND BIOLOGICAL ACTIV?

L13 44 DUP REM L11 (30 DUPLICATES REMOVED)
L14 30 S L13 AND PY<=2000
L15 0 S L14 AND HUVAC
L16 0 S L14 AND HUVEC

FILE 'STNGUIDE' ENTERED AT 18:59:29 ON 16 JUL 2003

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 19:00:21 ON 16 JUL 2003
L17 779 S VEGF C
L18 8 S L17 AND BIOLOG? ACTIVI?
L19 5 DUP REM L18 (3 DUPLICATES REMOVED)
L20 9 S L17 AND HUVEC
L21 9 DUP REM L20 (0 DUPLICATES REMOVED)
L22 9 S L21 NOT L19

=> s l17 and py<2000
2 FILES SEARCHED...
L23 211 L17 AND PY<2000

=> d bib abs

L23 ANSWER 1 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:530702 BIOSIS
DN PREV200000530702
TI Expression of angiopoietin-1 and -2 and their receptor tie-2 in renal cell carcinoma.
AU Theis, H. (1); Groene, H.-J. (1); Rabelink, T. J.
CS (1) Deutsches Krebsforschungszentrum, Heidelberg Germany
SO Kidney & Blood Pressure Research, (1999) Vol. 22, No. 4-6, pp. 206. print. Meeting Info.: Joint Scientific Meeting of the Society for Nephrology and the German Working Group for Clinical Nephrology Freiburg, Germany September 18-21, 1999
ISSN: 1420-4096.
DT Conference
LA English
SL English

=> d bib abs 2-10

L23 ANSWER 2 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:502196 BIOSIS
DN PREV200000487774
TI ***VEGF*** - ***C*** , VEGF-D and VEGFR-3 in tumor angiogenesis, lymphangiogenesis and metastasis.
AU Alitalo, K. (1)
CS (1) Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Helsinki Finland
SO Clinical & Experimental Metastasis, (1999) Vol. 17, No. 9, pp. 740. print. Meeting Info.: VIII International Congress of the Metastasis Research Society London, UK September 24-27, 2000
ISSN: 0262-0898.
DT Conference
LA English
SL English

L23 ANSWER 3 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:496269 BIOSIS
DN PREV200000496390
TI Expression of ***VEGF*** - ***C*** , VEGF-D and VEGFR-3 mRNA does not correlate with lymphatic spread in colorectal cancer.
AU George, M. L. (1); Tutton, M. G. (1); Jansen, F.; Eccles, S. A.; Swift, R. I. (1)
CS (1) Colorectal Dept., Mayday University Hospital, Surrey UK
SO Clinical & Experimental Metastasis, (1999) Vol. 17, No. 9, pp. 784. print. Meeting Info.: VIII International Congress of the Metastasis Research Society London, UK September 24-27, 2000
ISSN: 0262-0898.
DT Conference
LA English
SL English

L23 ANSWER 4 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:251909 BIOSIS
DN PREV200000251909
TI Vascular endothelial growth factor (VEGF) and ***VEGF*** - ***C*** show overlapping binding sites in embryonic endothelia and distinct sites in differentiated adult endothelia.
AU Lymboussaki, Athina; Olofsson, Birgitta; Eriksson, Ulf; Alitalo, Kari (1)
CS (1) Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Haartmaninkatu 3, Helsinki, 00014 Finland
SO Circulation Research, (***Nov. 26, 1999***) Vol. 85, No. 11, pp. 992-999.
ISSN: 0009-7330.
DT Article
LA English
SL English
AB Vascular endothelial growth factor (VEGF) is a key modulator of angiogenesis during development and in adult tissues, whereas the related ***VEGF*** - ***C*** has been shown to induce both lymphangiogenesis and angiogenesis. To better understand the specific functions of these growth factors, we have here analyzed their binding to sections of mouse embryonic and adult tissues and compared the distribution of the bound growth factors with the expression patterns of the 3 known members of the VEGF receptor family as well as with neuropilin-1, a coreceptor for VEGF165. Partially overlapping patterns of VEGF and ***VEGF*** - ***C*** binding were obtained in embryonic tissues, consistent with the expression of all known VEGF receptors by vascular endothelial cells. However, the most striking differences of binding were observed in the developing and adult heart, in which VEGF decorated all vessels, whereas strong ***VEGF*** - ***C*** signals were obtained only from epicardial vessels. In the lymph nodes, VEGF and ***VEGF*** - ***C*** showed distinct binding patterns in agreement with the differential location of their specific receptors. These results show that both ***VEGF*** - ***C*** and VEGF target embryonic blood vessels, whereas a more selective binding of ***VEGF*** - ***C*** occurs to its lymphatic vascular receptor in certain adult tissues. Our results suggest that VEGF and ***VEGF*** - ***C*** have both overlapping and distinct activities via their endothelial receptors.

L23 ANSWER 5 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:110145 BIOSIS
DN PREV200000110145
TI Current biology of VEGF-B and ***VEGF*** - ***C*** .
AU Olofsson, Birgitta (1); Jeltsch, Michael; Eriksson, Ulf (1); Alitalo, Kari
CS (1) Ludwig Institute for Cancer Research, SE-171 77, Stockholm Sweden
SO Current Opinion in Biotechnology, (***Dec., 1999***) Vol. 10, No. 6, pp. 528-535.
ISSN: 0958-1669.
DT General Review
LA English
SL English
AB Endothelial growth factors and their receptors may provide important therapeutic tools for the treatment of pathological conditions characterised by defective or aberrant angiogenesis. Vascular endothelial growth factor (VEGF) is pivotal for vasculogenesis and for angiogenesis in normal and pathological conditions. VEGF-B and ***VEGF*** - ***C*** provide this gene family with additional functions, for example, ***VEGF*** - ***C*** also regulates lymphangiogenesis.

L23 ANSWER 6 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:87144 BIOSIS
DN PREV200000087144
TI Vascular endothelial growth factor-C (***VEGF*** - ***C***) and its receptors KDR and flt-4 are expressed in AIDS-associated Kaposi's sarcoma.
AU Skobe, Mihaela; Brown, Lawrence F.; Tognazzi, Kathi; Ganju, Ramesh K.; Dezube, Bruce J.; Alitalo, Kari; Detmar, Michael (1)
CS (1) CBRC/Department of Dermatology, Massachusetts General Hospital, 13th Street, Building 149, Charlestown, MA, 02129 USA
SO Journal of Investigative Dermatology, (***Dec., 1999***) Vol. 113, No. 6, pp. 1047-1053.
ISSN: 0022-202X.
DT Article
LA English
SL English
AB Kaposi's sarcoma is characterized by clusters of spindle-shaped cells that are considered to be tumor cells and by prominent vasculature. Whereas spindle cells are most likely endothelial in origin, it remains controversial whether they are of lymphatic or blood vascular derivation. To test the hypothesis that the lymphangiogenesis factor vascular endothelial growth factor-C and its receptors, KDR and flt-4, are involved in the pathogenesis of Kaposi's sarcoma, we performed in situ hybridizations and immunofluorescent stainings on human immunodeficiency virus-associated Kaposi's sarcoma. Spindle-shaped tumor cells strongly expressed KDR and flt-4 mRNA. Immunofluorescent staining confirmed expression of the flt-4 receptor in Kaposi's sarcoma cells, and double labeling revealed its colocalization with the endothelial cell marker CD31. Vascular endothelial growth factor-C was strongly expressed in blood vessels associated with Kaposi's sarcoma. In vitro, human dermal microvascular endothelial cells also expressed vascular endothelial growth factor-C mRNA that was further upregulated by vascular permeability factor/vascular endothelial growth factor. Vascular endothelial growth factor-C potently stimulated the proliferation of Kaposi's sarcoma tumor cells in vitro. These results demonstrate important paracrine functions of vascular endothelial growth factor-C, produced by blood vessels, in the pathogenesis of cutaneous Kaposi's sarcoma, and suggest a lymphatic origin and/or differentiation of Kaposi's sarcoma tumor cells.

L23 ANSWER 7 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:69739 BIOSIS
DN PREV200000069739
TI Lymphangiogenesis and biological activity of vascular endothelial growth factor (***VEGF***)- ***C*** .
AU Mandriota, Stefano J. (1); Pepper, Michael S. (1)
CS (1) Departement de Morphologie, Centre Medical Universitaire, 1, rue Michel Servet, 1211, Geneve, 4 Switzerland
SO Journal de la Societe de Biologie, (1999) Vol. 193, No. 2, pp. 159-163.
ISSN: 1295-0661.
DT Article

LA French
SL English; French
AB Vascular endothelial growth factor (***VEGF***)- ***C*** is a new member of the VEGF family, a group of polypeptide growth factors which play key roles in the physiology and pathology of many aspects of the cardiovascular system, including vasculogenesis, hematopoiesis, angiogenesis and vascular permeability. VEGF signaling in endothelial cells occurs through three tyrosine kinase receptors (VEGFRs), expressed by endothelial cells and hematopoietic precursors. With respect to the first VEGF described, VEGF-A, which is an endothelial cell specific mitogen and key angiogenic factor, ***VEGF*** - ***C*** seems to play a major role in the development of the lymphatic system. This may reflect the different binding properties of VEGFs to VEGFRs, in that VEGF-A binds to VEGFR-1 and -2, whereas ***VEGF*** - ***C*** acts through VEGFR-3, whose expression becomes restricted to lymphatics and certain veins during development. However, the finding that ***VEGF*** - ***C*** also binds to and activates VEGFR-2 may explain why it induces angiogenesis under certain conditions, which makes it relevant to experimental or clinical settings in which one would wish to block or to stimulate angiogenesis. In this paper we briefly discuss current knowledge on the biological activity of ***VEGF*** - ***C*** , emphasizing that, as has already been shown for a number of other angiogenic factors, the biological effects of ***VEGF*** - ***C*** are strictly dependent on the activity of other angiogenic regulators present in the microenvironment of the responding endothelial cells.

L23 ANSWER 8 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:62940 BIOSIS
DN PREV200000062940
TI Expression of angiogenesis stimulators and inhibitors in human thyroid tumors and correlation with clinical pathological features.
AU Bunone, Giuseppe; Vigneri, Paolo; Mariani, Luigi; Buto, Simona; Collini, Paola; Pilotti, Silvana; Pierotti, Marco A.; Bongarzone, Italia (1)
CS (1) Division of Experimental Oncology A, Istituto Nazionale Tumori, 20133, Milan Italy
SO American Journal of Pathology, (***Dec., 1999***) Vol. 155, No. 6, pp. 1967-1976.
ISSN: 0002-9440.
DT Article
LA English
SL English
AB Experimental evidence has shown, both in vitro and in animal models, that neoplastic growth and subsequent metastasis formation depend on the tumor's ability to induce an angiogenic switch. This requires a change in the balance of angiogenic stimulators and inhibitors. To assess the potential role of angiogenesis factors in human thyroid tumor growth and spread, we analyzed their expression by semiquantitative RT-PCR and immunohistochemistry in normal thyroid tissues, benign lesions, and different thyroid carcinomas. Compared to normal tissues, in thyroid neoplasias we observed a consistent increase in vascular endothelial growth factor (VEGF), ***VEGF*** - ***C*** , and angiopoietin-2 and their tyrosine kinase receptors KDR, Flt-4, and Tek. In particular, we report the overexpression of angiopoietin-2 and VEGF in thyroid tumor progression from a prevascular to a vascular phase. In fact, we found a strong association between tumor size and high levels of VEGF and angiopoietin-2. Furthermore, our results show an increased expression of ***VEGF*** - ***C*** in lymph node invasive thyroid tumors and, on the other hand, a decrease of thrombospondin-1, an angioinhibitory factor, in thyroid malignancies capable of hematic spread. These results suggest that, in human thyroid tumors, angiogenesis factors seem involved in neoplastic growth and aggressiveness. Moreover, our findings are in keeping with a recent hypothesis that in the presence of VEGF, angiopoietin-2 may collaborate at the front of invading vascular sprouts, serving as an initial angiogenic signal that accompanies tumor growth.

L23 ANSWER 9 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:61157 BIOSIS
DN PREV200000061157
TI Placenta growth factor and vascular endothelial growth factor B and C expression in microvascular endothelial cells and pericytes. Implication in autocrine and paracrine regulation of angiogenesis.
AU Yonekura, Hideto; Sakurai, Shigeru; Liu, Xiaoxu; Migita, Hideyuki; Wang, Hua; Yamagishi, Sho-ichi; Nomura, Motohiro; Abedin, Md. Joynal; Unoki, Hiroyuki; Yamamoto, Yasuhiko; Yamamoto, Hiroshi (1)
CS (1) Dept. of Biochemistry, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa, 920-8640 Japan
SO Journal of Biological Chemistry, (***Dec. 3, 1999***) Vol. 274, No. 49, pp. 35172-35178.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB We have shown previously that vascular endothelial growth factor (VEGF) synthesized by the cellular constituents of small vessels per se, viz. endothelial cells and pericytes, participates in the hypoxia-driven proliferation of both cell types (Nomura, M., Yamagishi, S., Harada, S., Hayashi, Y., Yamashima, T., Yamashita, J., Yamamoto, H. (1995) J. Biol. Chem. 270, 28316-28324; Yamagishi, S., Yonekura, H., Yamamoto, Y., Fujimori, H., Sakurai, S., Tanaka, N., and Yamamoto, H. (1999) Lab. Invest. 79, 501-509). In this study, we examined the expression of the recently isolated VEGF gene family members (placenta growth factor (PIGF), VEGF-B, and ***VEGF*** - ***C***) in human dermal microvascular endothelial cells and bovine retinal pericytes cultured under various oxygen tensions. Quantitative reverse transcription-polymerase chain reaction analyses demonstrated that the two cell types possess not only VEGF (VEGF-A) mRNA, but also VEGF-B, ***VEGF*** - ***C*** , and PIGF mRNAs. Among them, only VEGF-A mRNA was induced under hypoxia. Competitive reverse transcription-polymerase chain reaction showed that, under normoxic conditions, the rank order of mRNA content in endothelial cells was PIGF > VEGF-B > ***VEGF*** - ***C*** > VEGF-A and that mRNA coding for PIGF was expressed at >100-fold higher levels than VEGF-A mRNA. In pericytes, the rank order was ***VEGF*** - ***C*** > VEGF-A > VEGF-B > PIGF, and apprx7-fold higher levels of ***VEGF*** - ***C*** mRNA compared with VEGF-A mRNA were noted in this cell type. Furthermore, anti-sense inhibition of PIGF protein production lowered the endothelial cell synthesis of DNA under hypoxic conditions. The results suggest that these VEGF family members may also take active parts in angiogenesis.

L23 ANSWER 10 OF 211 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:54357 BIOSIS
DN PREV200000054357
TI Vascular endothelial growth factor-C gene expression in papillary and follicular thyroid carcinomas.
AU Fellmer, Peter T.; Sato, Kanji; Tanaka, Reiko; Okamoto, Takahiro; Kato, Yoichiro; Kobayashi, Makio; Shibuya, Masabumi; Obara, Takao (1)
CS (1) Department of Endocrine Surgery, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, 162-8666, Tokyo Japan
SO Surgery (St Louis), (***Dec., 1999***) Vol. 126, No. 6, pp. 1056-1062.
ISSN: 0039-6060.
DT Article
LA English
SL English
AB Background. Vascular endothelial growth factor-C (***VEGF*** - ***C***) is known to be related to development of lymphatic vessels. Papillary thyroid carcinoma characteristically metastasizes to regional lymph nodes, whereas follicular thyroid carcinoma commonly spreads hematogenously. The present study was designed to determine whether expression of the ***VEGF*** - ***C*** gene is related to the different metastatic features of these 2 types of thyroid carcinoma. Methods. Thyroid carcinoma specimens were obtained from 15 patients with papillary carcinoma and 4 patients with follicular carcinoma of the thyroid. ***VEGF*** - ***C*** gene expression was examined by Northern blotting and in situ hybridization. Immunohistochemistry was performed to localize the deposition of ***VEGF*** - ***C*** protein. Results. The ratios of ***VEGF*** - ***C*** gene expression determined by Northern blot analysis were significantly higher in papillary than in follicular carcinoma. Nonmalignant thyroid tissue from patients with papillary carcinoma also expressed higher levels of ***VEGF*** - ***C*** than tissue from patients with follicular carcinoma. Expression of the ***VEGF*** - ***C*** gene was observed by in situ hybridization in cells of papillary thyroid carcinoma but not in those of follicular carcinoma. Positive staining with antibody against ***VEGF*** - ***C*** was detected in papillary cancer cells. Conclusions. Concurrent overexpression of the ***VEGF*** - ***C*** gene by both tumor cells and the surrounding tissue may be related to the prevalence of intrathyroidal spread through lymphatics and regional lymph node metastasis in patients with papillary thyroid carcinoma.

=> FIL STNGUIDE
COST IN U.S. DOLLARS

	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		66.53	223.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL

	ENTRY	SESSION	
CA SUBSCRIBER PRICE		-1.30	-3.90

FILE 'STNGUIDE' ENTERED AT 19:06:47 ON 16 JUL 2003

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 11, 2003 (20030711/UP).

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COST IN U.S. DOLLARS

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FULL ESTIMATED COST	0.06	223.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL

	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-3.90

STN INTERNATIONAL LOGOFF AT 19:07:04 ON 16 JUL 2003